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GENETIC PROBLEMS IN MINK CULTURE

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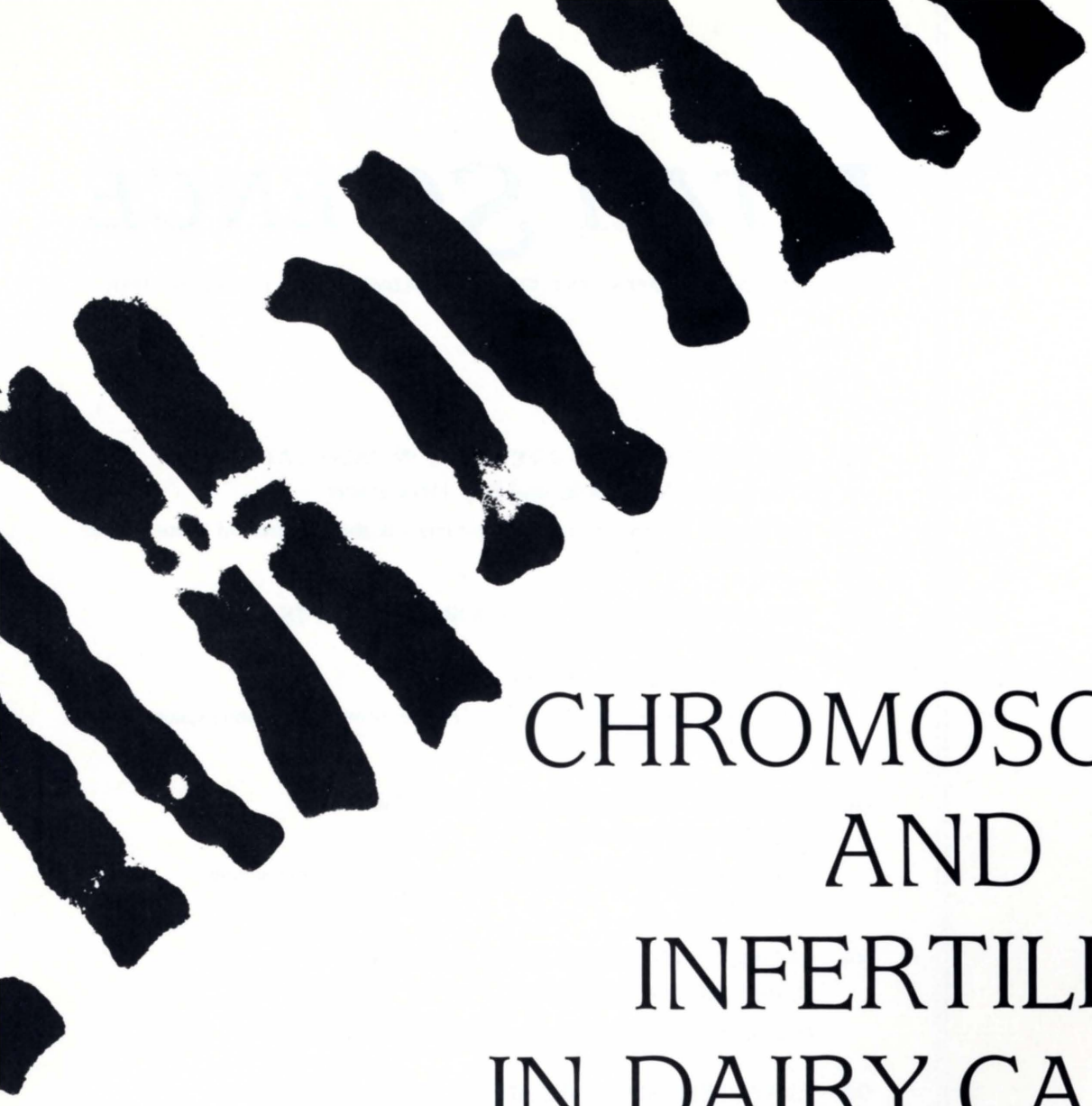
COVER: Jim Colby holds a mink raised at the Gary R. Egbert Mink Farm, Lewiston, Utah.
Photo by: Gary Neuenswander



CHROMOSOMES AND INFERTILITY IN DAIRY CATTLE

T. D. BUNCH, A. MACIULIS and S. L. HENDERSON

FIGURE 1. *Bos taurus* bull has 60 chromosomes with a karyotype that consists of 58 autosomal acrocentrics, a large biarmed X and a small biarmed Y.

The study of chromosomes increased greatly when technical developments during the 1950s let biologists, veterinarians and livestock scientists more readily observe the mammalian chromosome. Aberrations in chromosome number or structure are now known to cause sterility, reduce fertility, embryonic or fetal death, stillbirths and/or congenital malformations. In humans, there are 200,000 spontaneous abortions of chromosomally abnormal fetuses annually in the U.S.; one of 100 newborn babies has some type of chromosome defect.

There has been concern that the use of new techniques such as superovulation, ova collection, *in vitro* fertilization, embryo transfer, gene transfer, cloning, and embryo micromanipulation may increase the risks of chromosome/embryo/fetal abnormalities. The popularity of artificial insemination in the cattle industry increases the risk that a chromosomal defect in one bull will be carried by hundreds of thousands of its offspring. A better understanding of the role of chromosome aberrations in mammalian reproduction can help determine the risk/benefit ratio of using these technologies and how often these defects normally occur in animals.

The chromosome is the organelle that stores, replicates and transmits the genetic information (genes) of biological inheritance. Chromosome functions are regulated so chromosome products appear at the right time and in the appropriate amounts during the life of the organism. In specialized organs (testicles and ovaries) the genetic content of chromosomes are rearranged so the species is maintained, yet progeny have unique characteristics. Every organism, whether a virus, a bird or a cow, has a unique set of chromosomes.

Karyotype of Cattle Chromosomes

Cattle, both *Bos taurus* and *Bos indicus*, have 58 autosomes (nonsex chromosomes) and two sex chromosomes (two X chromosomes in the female and one X and one Y chromosome in the male) (Figures 1 and 2). Cattle chromosomes range in size from less than 1 micrometer (1/1000 of a meter) to somewhat larger than 4 micrometers.

A karyotype is an arrangement of chromosomes by size, from the largest to the smallest (Figure 1). A diagram of the karyotype (an idiogram) is based on chromosome structure and size (Figure 3). The cattle karyotype consists of 29 pairs of acrocentric autosomes and one pair of sex chromosomes. The sex chromosomes in the female consist of two large biarmed or metacentric X chromosomes. In the male, the sex chromosomes consist of one biarmed X (as in the female) and either a small acrocentric, submetacentric or metacentric Y chromosome. The only visible difference between *B. taurus* and *B. indicus* chromosome is in the Y chromosome; it is the smallest acrocentric in *indicus* and a small submetacentric or metacentric in *taurus*.

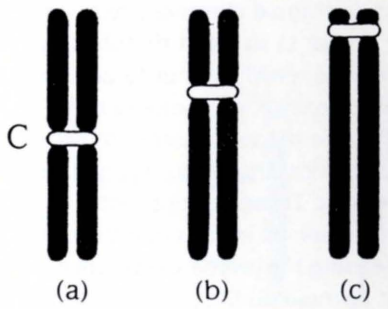


FIGURE 2. Chromosome types are determined by position of the centromere (C).

a. metacentric: centromere located near center of chromosome producing a biarmed configuration.

b. submetacentric: centromere between middle and end of chromosome, also producing a biarmed configuration.

c. acrocentric: centromere near end of chromosome giving the appearance of a single-arm configuration.

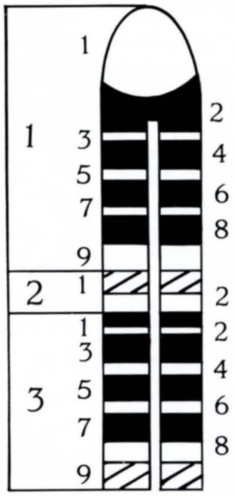


FIGURE 3. The idiogram is a diagramatic representation of the chromosome. Light and dark regions are given specific ascriptions so that chromosome changes can be precisely described. The idiogram of the cow consists of 29 acrocentrics, two submetacentric X's in the female, or a submetacentric X and a Y chromosome in the male. Only chromosome 1 of the idiogram is represented in this figure.

FIGURE 4. G-band karyotype of *Bos taurus*. Each pair of chromosomes has a unique pattern of light and dark bands that distinguishes it from the other pairs of chromosomes within the karyotype.

TABLE 1. Breeds in which the 1/29 translocation has been reported.*

Austrian Simmental	Limousin
Baoulé	Marche
Blonde Aquitaine	Modica
British White	Montbeliard
Brown Atlas	Norwegian Red
Brown Mountain (West Germany)	Oberinntal (Austrian) Gray
Brown Swiss	Pisa
Charolais	Podolian
Chianina	Polish Red
Czechoslovakian Red Pied	Red Poll
Gascony	Romagna
German Red Pied	Russian Black Pied
German Simmental	Santa Gertrudis
Guernsey	Siamese
Hungarian Gray	Simmental
Hungarian Simmental	Swedish Red and White
Japanese Black	Swiss Brown
Kuban (Zebu)	Thai
Kuri	Vosges

*From Eldridge, 1985.

Banding techniques developed during the late 1960s and early 1970s (C-banding, G-banding, Q-banding and R-banding) helped delineate the differences among mammalian chromosomes. Individual chromosomes, even those similar in size and morphology, can now be readily identified and their structures examined. Banding techniques have made it possible to precisely describe chromosomes of domestic livestock. These developments were a major impetus in the organization of the Reading Karyotype Conference, which formulated the standard karyotype for all major species of livestock. Figure 4 illustrates a G-banded karyotype for cattle and shows the dark and light banding patterns associated with each chromosome.

Chromosomes are remarkably constant from one cell to the next or from one generation to the next. This constancy is essential in preservation of a species. However, chromosomes do undergo change spontaneously and equal numbers of chromosomes sometimes fail to segregate to daughter cells. Under normal conditions, such changes are rare, and when they do occur, they usually result in reproductive failure or offspring with physical impairments. In cattle, there are two major types of chromosome variation: variation in chromosome number and variation in chromosome structure.

Variations in Number of Chromosomes

Numerical chromosome deviations involving the autosomes (monosomy, loss of one or more chromosomes; or trisomy, the addition of one or more chromosomes) are rarely observed and are probably eliminated early in pregnancy. On occasion, however, animals with trisomies have been born and are usually severely deformed (Gustavsson 1984). Examples of these chromosome aberrations in cattle are an extra chromosome 18, which results in nanism (dwarfism), and an extra chromosome 17, which results in a wide spectrum of complex malformations, of which branchygnathia inferior (an unusually short lower jaw) is most common anomaly. As in humans, a monosomic condition is fatal and rarely does an affected fetus go to term. These types of chromosome aberrations are of little significance to the cattle industry unless they occur fairly often.

Although the number of autosomal chromosomes does not usually vary in cattle, deviations in the number of sex chromosomes occur and are related to abnormal sexual development. In general, apart from the effect of the X and Y chromosomes on the reproductive system, the effects of variation in these two chromosomes are less severe than those induced by autosomal trisomies and monosomies. Variations in

sex chromosomes are usually not fatal to the embryo or the newborn calf. Various types of deviations in the number of sex chromosomes have been reported in cattle (i.e. XO, XXY, XYY, XX/XY, XX/XXY, XXX, XXX/XY etc.) which have resulted in testicular and ovarian hypoplasia (incomplete development), gonadal dysgenesis (defective development) and intersexuality (reproductive organs of both sexes) (Hare and Singh 1979). These types of chromosome aberrations have no long-term affects on the cattle industry other than causing partial or complete infertility in affected animals.

TABLE 2. Robertsonian Translocations identified in cattle.*

Chromosomes	Breed
1/4	Czechoslovakian cattle
1/23	Czechoslovakian cattle
1/25	Simmental
1/28	Czechoslovakian cattle
1/29	38 different breeds
2/4	Friesian
2/8	British Friesian
3/4	Limousin
3/27	Friesian
5/18	Simmental
5/21	Japanese Black
5/23	Romanian Brown
6/16	Dexter
6/28	Czechoslovakian cattle
7-11/20-25	Blonde Aquitaine X Limousin
7/12	Japanese Black
7/21	Japanese Black
8/9	Swiss
10/15	Petanqueiras
11/16	Hungarian Simmental
11-12/15-16	Blonde Aquitaine k-X Simmental
11/21	Romanian Brown cattle
11/22	Czechoslovakian cattle
13/21	Holstein-Friesian
14/21	Swiss Simmental
14/24	Podolian
14/28	Holstein
25/27	Alpine Gray
27/29	Guernsey

Chromosomes 17, 19 and 26 have not yet been observed in translocations.

*From Eldridge, 1985 and Gustavsson, 1985.

Although Freemartinism is not a direct consequence of deviations in sex chromosomes, it can be verified by chromosomal techniques. Freemartinism mainly occurs in cattle, although it has been documented in sheep, goats, pigs and horses (Hafez 1968). Freemartinism occurs during a multiple pregnancy when the chorioallantois of adjacent embryos of opposite sexes fuse. Freemartins have internal reproductive organs of both sexes; a modified ovary somewhat similar to the male gonad and external genitalia like those of a normal female. In 90-95 percent of cases, the female co-twin is sterile, and the male may be normal, somewhat fertile, or sterile. Leucocytes from Freemartins contain a mixed population of cells with XX and XY chromosomes.

Variation in Chromosome Structure

Variation in chromosome structure has a greater effect on the cattle industry than variations in number. In 1964, Gustavsson and Rockborn reported the first clearly observable chromosomal structural change in cattle while studying lymphatic leukemia in cattle. They identified the structural aberration as a centric fusion and referred to it as a 1/29 Robertsonian translocation (Figure 5). The 1/29 translocation in Swedish Red and White Cattle reduced fertility by 5-8 percent. This decrease is associated with an early return to service and is assumed to result from nondisjunction (the irregular distribution of chromosomes) during meiosis. Since Gustavsson's original discovery, the 1/29 translocation has been found in 38 breeds of cattle (Table 1) throughout the world (Eldridge 1985). In Sweden, elimination of 1/29 bulls from artificial-insemination programs has increased fertility in the Swedish Red and White breed. Countries such as Australia now require that all imported bulls be screened for the 1/29 translocation.

The 1/29 translocation may have

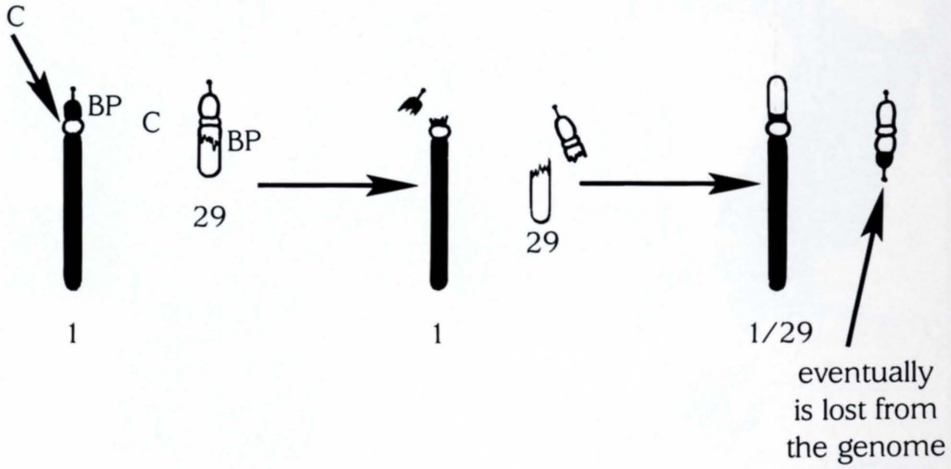


FIGURE 5. Possible explanation of the 1/29 translocation in cattle. Breakpoints (BP) occur in the heterochromatic regions close to the centromere (c) in acrocentric chromosomes 1 and 29. Translocation products are a submetacentric (biarmed) chromosome and a very small metacentric chromosome that is lost without genetic consequence to the animal.

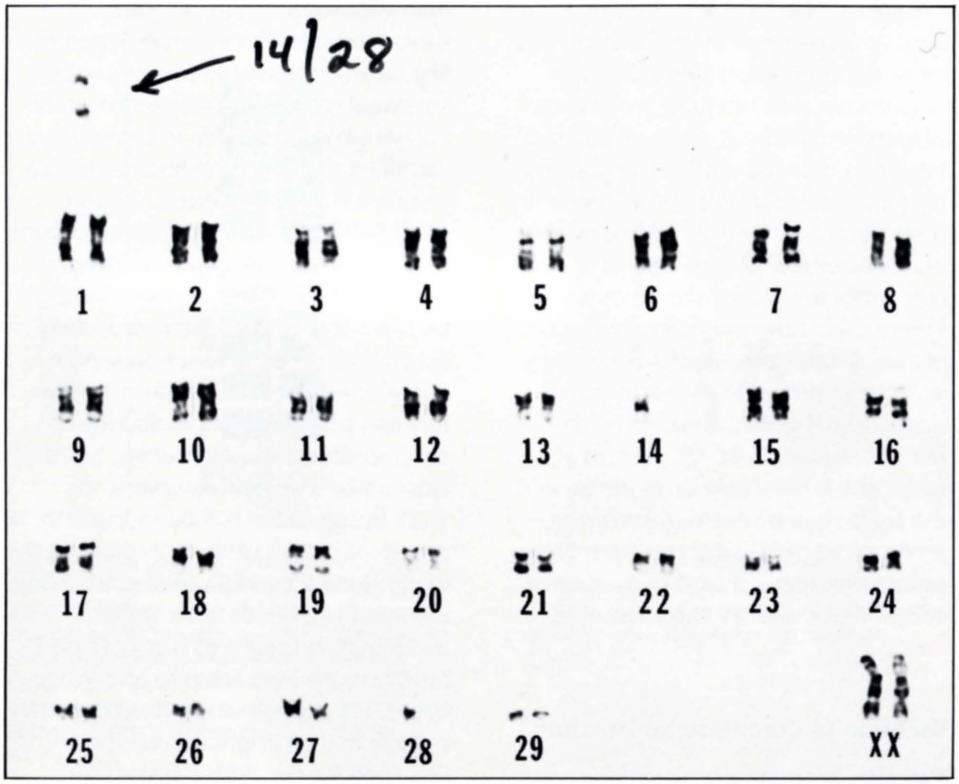
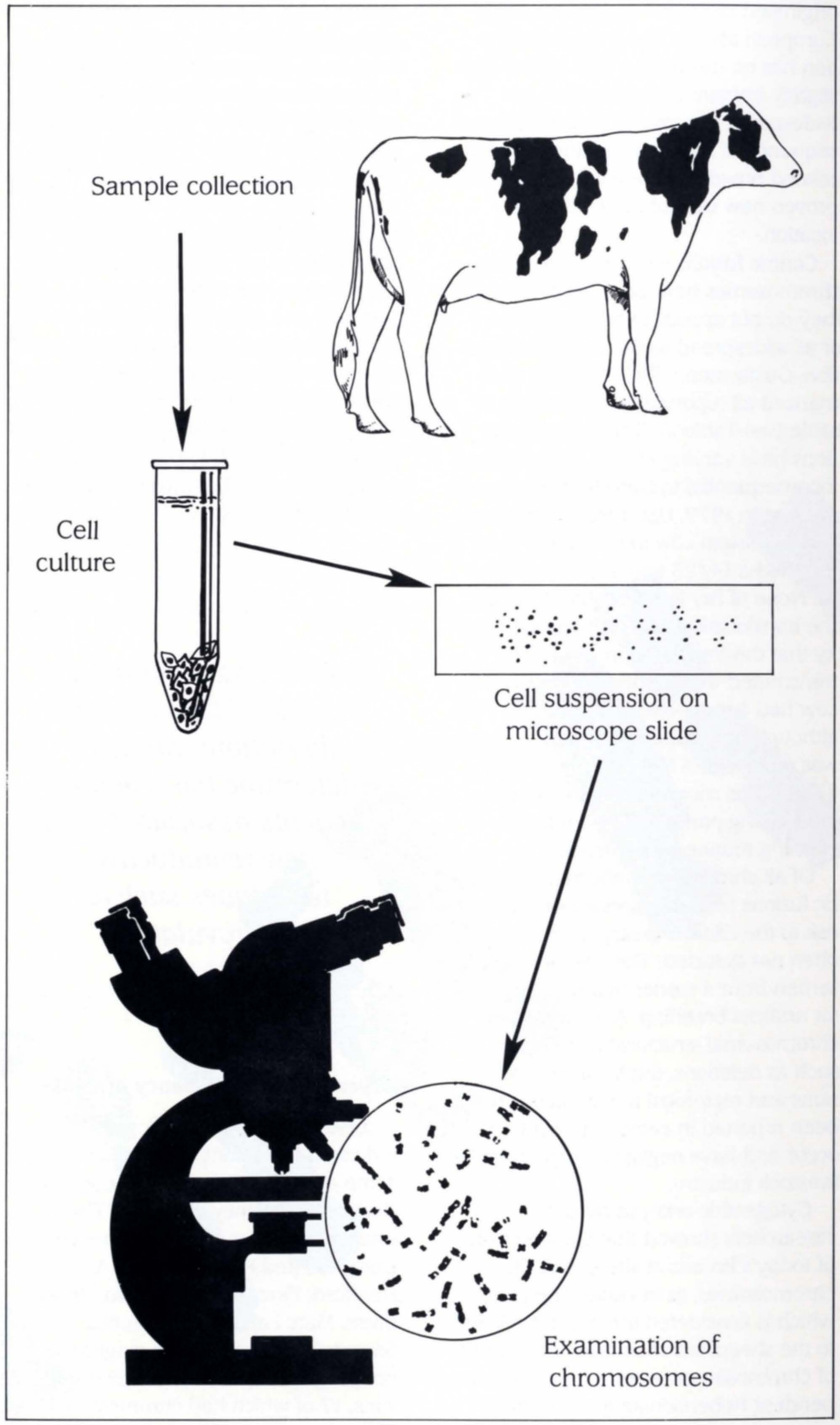


FIGURE 6. Karyotype of a Holstein cow with a 14/28 translocation. Chromosomes 14 and 28 are unpaired as compared to the other chromosomes. The translocation chromosome is a submetacentric (biarmed) chromosome. During meiosis (process involved in the normal development of the ovum or sperm) chromosomes 14, 28 and 14/28 must come together, pair and then segregate properly. If this process fails, then the resulting gametes are genetically unbalanced. This phenomenon is believed to be the main cause of infertility in cows with translocations.

FIGURE 7. Holstein cow with 14/28 translocation. The head of the affected cow (right) is wider between the eyes and shorter from the crown to the tip of the nose. The cow on the left has a head typical of the Holstein breed.

FIGURE 8. Samples are collected from the tall vein. Ten-twelve drops of blood are placed in culture medium for 4 days. Within the blood are specialized cells called leucocytes. They are stimulated and synchronized in their cell division. The cells are harvested at the end of 4 days, placed upon microscope slides, their chromosomes treated to produce bands and then stained. Chromosomes are examined at 1,000 times (1000 X) their normal size with the use of a microscope.



originated centuries ago from a single European source. Since the translocation has no deleterious effect other than slightly impairing reproduction, its widespread occurrence may be a consequence of the result of inheritance in related breeds. There has been no other proven new case of the 1/29 translocation.

Centric fusions involving other cattle chromosomes have been reported, but they do not appear to be as significant or as widespread as the 1/29 translocation. Gustavsson (1985) recently summarized all reported centric fusions in cattle (see Table 2). These translocations have varying effects, ranging from inconsequential to considerable physical defects. In 1979, USU researchers identified a Holstein cow in their dairy herd that had a 14/28 translocation (Figure 6). None of her living offspring carried the translocation, although the probability that the translocation would be transmitted was 50 percent or less. The cow had a male-like appearance although her reproductive performance was typical for a Holstein cow (Figure 7). She was more difficult to handle in the milking parlor and had difficulty in learning routine movements.

Of all chromosome aberrations, centric fusions probably present the greatest risk to the cattle industry since they are often not detected. The risk increases if semen from a carrier bull is widely used for artificial breeding. Although other chromosomal structural aberrations such as deletions, duplications, inversions and reciprocal translocations have been reported in cattle, they seldom occur and have negligible impact on the livestock industry.

Cytogenetic analysis by USU researchers showed that the ancestors of today's breeds of sheep had 60 chromosomes, as in cattle. The goat, which is considered the nearest relative to the sheep, still maintains this number of chromosomes. A series of three independent Robertsonian translocations reduced the chromosome number in sheep from 60 to 54. Centric fusions have been the principal mechanism of chromosome evolution and change in sheep. The Romney-Drysdale breed of sheep in New Zealand is undergoing further changes in chromosome number due to a recent series of centric fusions. Researchers at USU and New Zealand are determining why this group of sheep is chromosomally unstable and what mechanisms are involved in the changes. We have found that, with few exceptions, the chromosome banding patterns of cattle and sheep are very similar. Information from this cooperative study may provide insights into possible causes of chromosome change in cattle.

A better understanding of the role of chromosome aberrations can help determine the risk and benefits associated with new reproductive techniques such as superovulation.

Reproductive Inefficiency in Cattle

A survey by Swartz and Vogt in 1973 indicated the extent to which chromosome abnormalities might cause reproductive inefficiency in heifers. They examined heifers of the Simmental, Gelbvieh, Red Poll, Charolais, Angus, Hereford, Pinzgauer, Limousin, Brown Swiss, Marc I and Marc II breeds. Seventy-one heifers were diagnosed nonpregnant after two breeding seasons, 17 of which had chromosomal aberrations that probably caused infertility. The chromosomal abnormalities included one tetraploid/diploid mosaic (different chromosome sets in the same animal), five possible 1/29 translocations, two trisomy 59, XO/60,XX mosaics, one 60, XX/60,XY chimera (tissues from different sources, such as Freemartinism) and two mixoploid mosaics (cell populations with different numbers of chromosomes) with chromosomal designations of 59,XXXO/60, XX/61,XXX and 59,XO/60,XX/61,XO. Seventy-one fertile females were of the same ages and breeds had normal chromosomes. In a similar survey, Gustavsson (1971) reported that 30.8 percent of 263 repeat breeder heifers from Swedish herds carried a 1/29 translocation.

These results indicate that chromosomal abnormalities may significantly lower fertility. The USU Department of Animal, Dairy and Veterinary Sciences initiated a study to determine whether some type of reproductive inefficiency can be associated with chromosome abnormalities in dairy heifers and, if so, whether the aberrations are inherited. Reproductive inefficiency is one of the more difficult problems confronting dairymen today. The average dairyman culls 22 percent of the heifers in a herd due to reproductive inefficiency. This represents 2-3 percent of all heifers in a dairy herd.

The survey will involve 150 Holstein heifers from three groups. Group 1, the control group, consists of heifers that have been diagnosed pregnant that have had no more than two A. I. services within 42 days, or those that have been bred by a bull within the same time period. Group 2 will consist of heifers that have been diagnosed pregnant following three or more A.I. breedings or that were exposed to a fertile bull during a similar 63-day breeding period. In Group 3 are heifers that have been artificially inseminated at least four times, or that were exposed to a

fertile bull in a similar 84-day breeding period that have not been diagnosed as pregnant. Chromosome surveys will be based on 72-hour leucocyte cultures (Figure 8). Any apparent chromosome aberration will be identified using chromosome-banding techniques.

This project is about one-eighth completed. Eighteen cows representing all three groups have been examined and none have exhibited any chromosome abnormalities.

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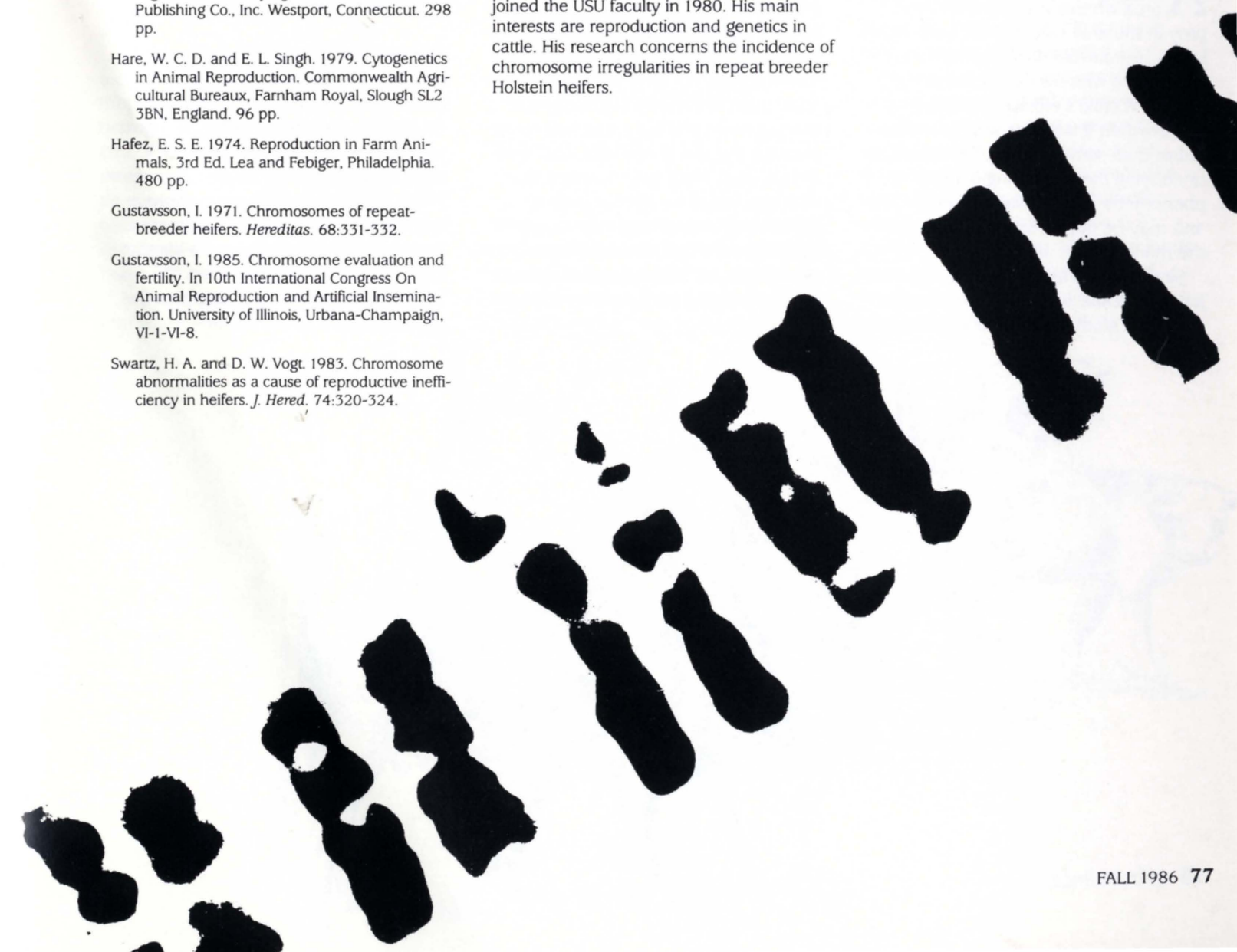


THE APPLICATION OF BEHAVIORAL CONCEPTS TO LIVESTOCK MANAGEMENT

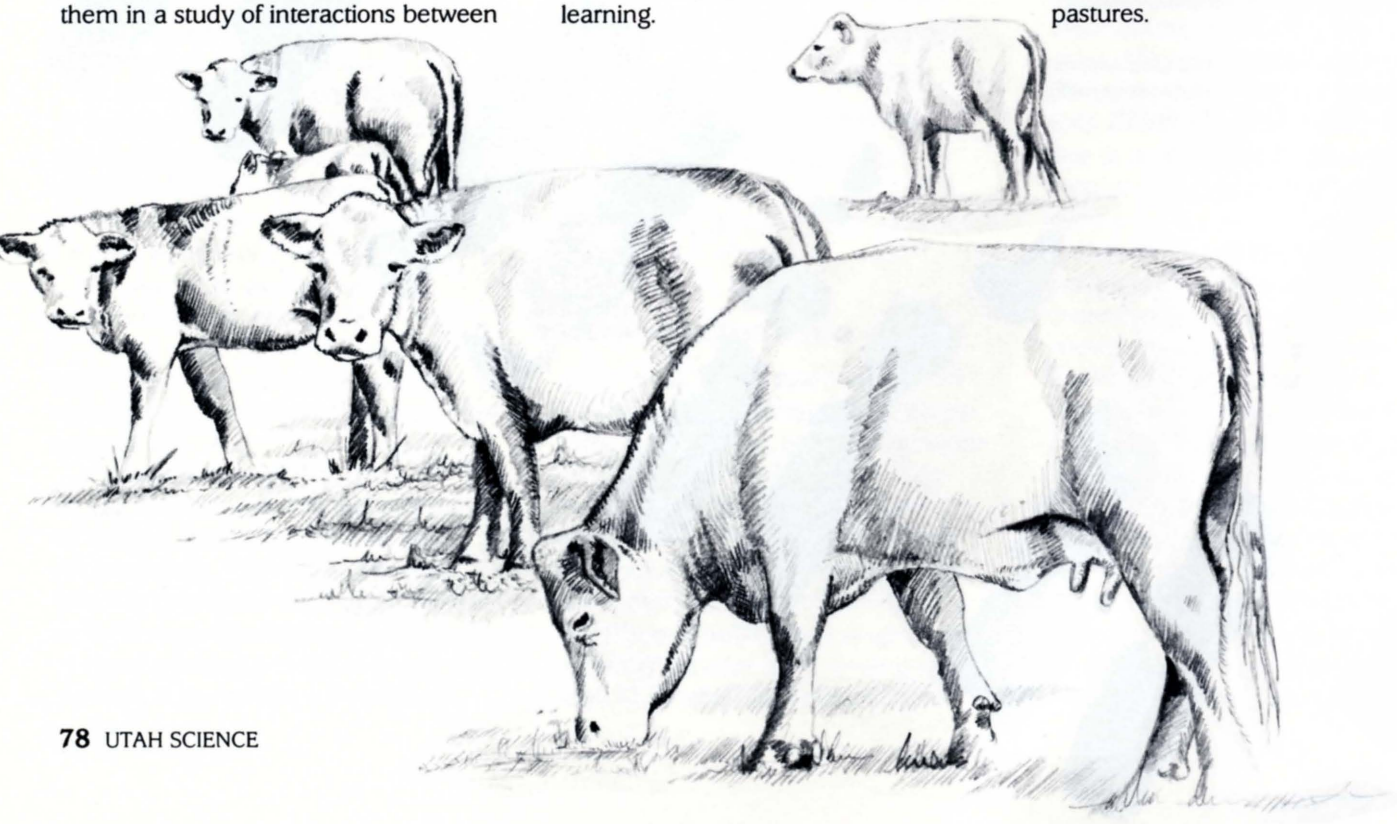
D. F. BALPH and M. H. BALPH

A coyote moves to a new hunting area when it is less likely to find prey in the area where it has been hunting. A 16-hour-old duckling becomes attached to whatever object is moving nearby. A child's efficiency of learning is higher when it interacts with its mother rather than someone else. The concepts underlying these seemingly disparate phenomena govern many aspects of life and may be of practical significance in the management of livestock.

Several years ago, USU range scientist John Malechek suggested that we join them in a study of interactions between livestock and rangelands. He believed that animal behaviorists such as ourselves might have useful insights on the behavioral response of animals to plant communities. We were interested in the application of behavioral principles to management problems, but had never pursued this line of research. Our work always dealt more with concepts than with species, so we felt our findings concerning wildlife might also apply to livestock. Although we had not previously worked with livestock, we had studied foraging behavior and animal learning.

Short-Duration Grazing

The first such research program concerned short-duration grazing on crested wheatgrass at Tintic, Utah (Malechek and Dwyer 1983). This grazing system involves movement of a large herd of animals through a series of small pastures; animals spend only a few days in each pasture. The pastures are usually clustered around a central corral where water is provided. The corral is also used to control access to the pastures.



Advocates of short-duration grazing believe the system increases the carrying capacity of the range. They also belive animals may be more uniformly distributed on the range and existing plant species are more fully used than with conventional grazing methods. Although short-duration grazing has attracted considerable attention and is practiced on some ranches, there was little objective information about its consequences for the land, plant communities, and livestock. The research conducted at Tintic studied the effects of short-duration grazing with Angus heifers. Our role was to assess the impact of behavior in this grazing system.

There were several behavioral aspects associated with short-duration grazing that interested us, one which we believed might be particularly important. The repeated, rapid depletion of the forage coupled with moving the cattle every three days to an adjacent area with abundant forage might not be compatible with efforts to make maximum use of forages.

Experimental psychology suggests that when animals are given rewards at regular intervals (fixed-interval reinforcement schedule), they will learn the time-dependent nature of the rewards and behave appropriately as the time for the reward approaches. The cattle, therefore, could be expected to anticipate being moved to an area with more abundant forage every three days.

Cattle and other animals that live in groups must choose between group and individual activities. The conflict seems to affect grazing behavior.

The second relevant concept is found in behavioral ecology and is based on the premise that evolutionary pressure has promoted foraging efficiency (optimal foraging theory). As an animal feeds in a particular area, the food supply declines. Eventually the animal will leave for a new area in which food is more abundant (patch give-up time). Theoreticians have calculated that the optimal time to move is when the value of the food patch is less than the average value of patches it has already grazed, minus the cost of moving to a new patch.

The cattle, of course, cannot move when they wish, but they may sense when they should move. The ability of cattle to anticipate the time of the move may result in decreased foraging. Cattle need not forage extensively every day because of their large body size. Moreover, they need not graze each pasture evenly and intensively.

An obvious way to prevent a premature decline in grazing motivation is to base moves to a new pasture according to forage abundance instead of time—exactly what is recommended for short-duration grazing. Animals would then learn that a move to another pasture occurs when the forage in the pasture they currently graze reaches some predetermined level, which could be the level recommended

for short-duration grazing. The forage cue could also be enhanced by having pastures of different sizes and by altering (to the extent feasible) the sequence in which pastures are grazed.

At Tintic, Ken Olson and Jerry Rouse, graduate students in the Department of Range Science, have collected data concerning grazing motivation over time in a pasture. Their preliminary results support the hypothesis that the cattle lose some interest in grazing on the day they are to be moved (the third day). The cattle also gather at the corral as the time to move approaches. The decrease in foraging in anticipation of the move to a new pasture is not as great as we had anticipated, perhaps due to a conflict between group-based and individual-based decision rules.

Gregariousness and Social Facilitation

Behavior of animals that live in groups is, to varying degrees, governed by two rules: gregariousness (the desire to be with friends) and social facilitation (the desire to mimic the activity of friends). Individuals in the group also act to satisfy their own needs, such as drinking when thirsty. The behavior of the heifers studied at Tintic often indicated that they experienced a conflict between individual and group determinants of behavior. For example, an animal might decide to stop foraging until the gate to the new pasture opened. Later, however, the desire to join other cattle might mean it joins a group of foraging animals and begins feeding again.

The conflict animals experience between the two types of behavior may be more pronounced in short-duration grazing where animal density is increased. There are too many animals to form a single social unit, and too little space for social units to be independent of one another. As a result, cattle are dispersed and tend not to graze in synchrony, behavior that may promote more uniform use of the pasture. This is one goal of short-duration grazing.

Effects On Plants

Another goal of short-duration grazing is to aid plants in obtaining water and nutrients. This might be accomplished when cattle hooves break up the soil surface and mix litter with soil. We observed, however, that this might not occur in our pastures due to the nature of crested wheatgrass and the behavior of heifers (Balph and Malechek 1984).

Crested wheatgrass grows in tussocks that are usually elevated from the surrounding soil. Litter and algal crusts are generally associated with the tussocks and the surrounding soil is bare. We noted that cattle seemed to avoid stepping on the tussocks. This avoidance of

TABLE 1. The observed and expected frequency of cattle hoofprints on and near crested wheatgrass tussocks.

	Number of hoofprints	
Hoofprint location	**Observed**	**Expected**
Plots (1 m^2, n = 16)		
On tussocks	15	71
On bare ground	273	217
Tussock elevation		
1-3 cm	10	33
4-6 cm	5	21
6 > cm	0	21

tussocks might be based on the fact that skeletal strength does not increase in direct proportion to body mass. Species with larger body size should pay more attention to footing than those with smaller mass. Obviously, a cow is a relatively large animal.

If heifers were avoiding uneven surfaces of tussocks to avoid poor footing, then there should be disproportionately more hoofprints in the open spaces between tussocks than on tussocks. Also, the more tussocks were elevated, the less they should be trampled.

To test these hypotheses, we established two transects perpendicular to the radial fences in a pasture. One transect was 75 meters and the other was 150 meters from the central corral. After cattle were removed from the paddock, a frame 1 meter square was placed at 5-meter intervals 10 times on the near transect and six times on the far transect. We then marked all hoofprints, mapped the location of crested wheatgrass tussocks, measured the distance tussocks were above the surrounding substrate, and recorded the location of each hoofprint on the tussock map.

We then placed a dot matrix overlay on the 16 mapped plots and found that 26 percent of the area was covered with crested wheatgrass tussocks; the remaining area was bare ground. If hoofprints occurred at random on the 16 plots, 71 hoofprints would have been found on tussocks (Table 1). However, only 15 hoofprints were found on tussocks, significantly fewer than expected. Thus, the data indicate that heifers deliberately avoid stepping on tussocks.

Young animals have a remarkable ability to learn, and to remember what they have learned. That ability may be useful in molding their dietary preferences.

There were also significantly fewer hoofprints on the more-elevated tussocks than on those that were not as high (Table 1). The results support our hypothesis that cattle avoid elevated tussocks. Results also indicate that the hoof action thought to be of benefit in short-duration grazing was of little significance in crested wheatgrass pastures.

Molding Foraging Behavior

We are also interested in determining whether livestock foraging behavior can be molded to fit environments that the animals will later encounter, e.g. desert range or feedlot. The investigation began about three years ago under the leadership of Fred Provenza of the Department of Range Science and is supported by the Utah Agricultural Experiment Station and USDA. The study involves exposing young livestock to foods that they will encounter as adults. We are fairly certain that livestock diets are influenced by the feeds animals are exposed to early in life; we are therefore determining the extent of this influence and whether it is economically feasible to train animals to eat certain diets.

THE APPLICATION OF BEHAVIORAL CONCEPTS TO LIVESTOCK MANAGEMENT

The behavioral concepts of imprinting and social modeling may be related to learning efficiency. Imprinting, a type of learning first described by European animal behaviorists in the 1930s, occurs during a sensitive period in an animal's life; whatever an animal learns during that period tends to persist. This form of learning is quite common. Examples include such phenomena as salmon returning to spawn where they hatched and the tendency of ewes to reject all but their own lambs.

Imprinting

The importance of imprinting can be described in a natural-history context. For example, a male songbird born in the north flies south for the winter, often in mixed-species flocks, and returns north to the breeding grounds in the spring. It must sing a dialect of its species-specific song to attract a mate. Natural selection has given the young bird, when it is about two months old, the ability to learn and remember any bird song it hears. In the natural environment, a two-month-old male invariably hears and learns the song of its father.

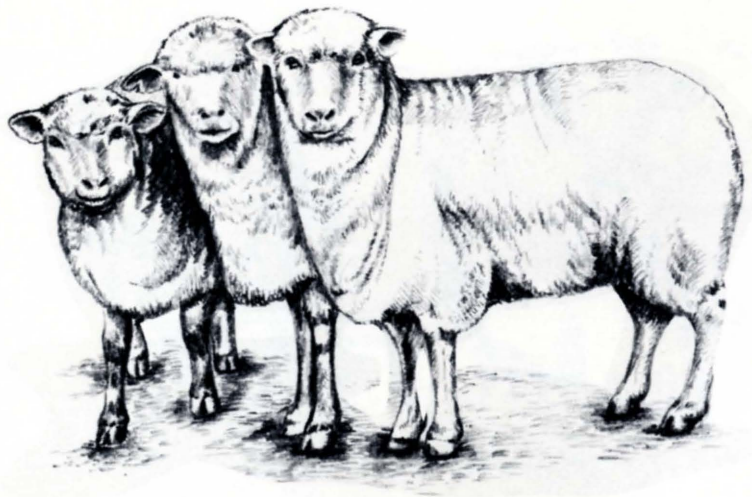
Briefly feeding certain feeds to young livestock during sensitive periods may permanently influence what feeds they like or dislike.

Such a "window" for learning what to eat could also exist in livestock. If so, it would mean that a young animal need not learn what is appropriate to eat by trial and error, an inefficient and potentially dangerous method of learning. Instead, it can learn from its mother, an experienced forager. The most appropriate time for such learning to occur is during weaning when the young animal is capable of eating a variety of vegetation but is not yet independent of its mother. Ron Squibb, a graduate student in the Department of Range Science, has discovered that lambs apparently are sensitive to learning food preferences during weaning at four to eight weeks of age. Thus, it may be possible to permanently influence diet selection by briefly exposing lambs to certain feeds during the sensitive period.

Social Modeling

Social modeling has its origins in child psychology and concerns the role of interactions with others (social models) in teaching children. A child seems to learn most efficiently when it is interacting with another person, especially a nurturant such as its mother.

Anna Gudrun Thorhallsdottir, a student in the Department of Range Science, has tested whether social modeling influences lambs' preferences for novel foods. In experiments, lambs either watched other animals (the mother, a familiar adult, or a familiar lamb) eat these feeds, or actually ate the feed with these animals. The results



were consistent with social modeling theory: The lambs' subsequent diets were most influenced by interactions with the mother while eating; the least influential interactions were observations of peers. Thus, there is now evidence that both social modeling and imprinting enhance an animal's learning efficiency. These results increase the likelihood that it may be economically feasible to tailor an animal's dietary preferences to available feeds, although much more research is necessary to confirm the hypotheses.

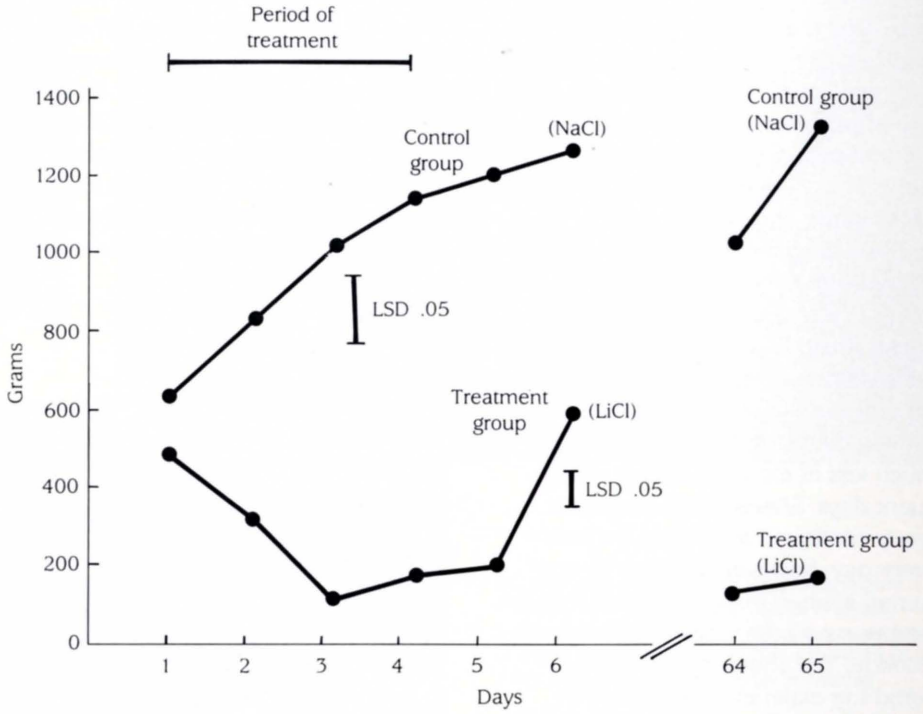
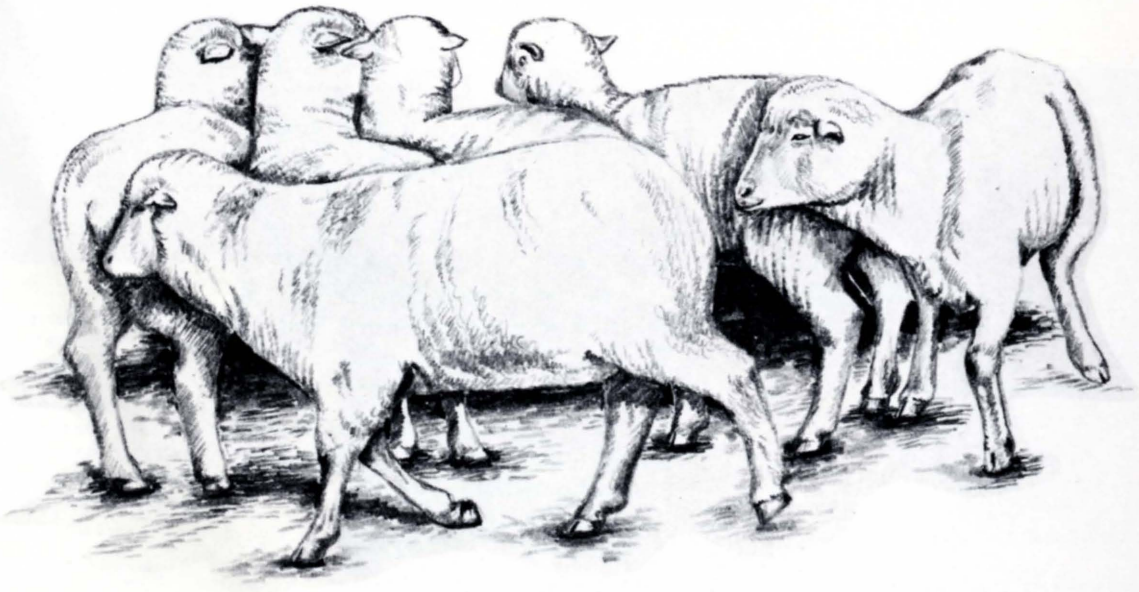


FIGURE 1. Amount of barley eaten by treatment and control groups. Note the decrease in consumption by sheep that ate the tainted feed, the increase in consumption when food was no longer tainted, and the persistence of what was learned (after Thorhallsdottir, Provenza and Balph).

Taste-Aversion Learning

It would be extremely beneficial if livestock could be taught not to eat certain feeds, such as poisonous plants. The concept of taste-aversion learning, which has been studied extensively by psychologists, is appropriate to this type of learning. It has been shown that sheep can be taught to avoid a particular food if eating the food has unpleasant gastronomic consequences (Thorhallsdottir, Provenza and Balph, in



press). Olsen and Ralphs (in press) of the Poisonous Plant Laboratory (USDA) have achieved the same results with cattle. The learning is somewhat analogous to a child who develops a distaste for grape juice after consuming a mixture of castor oil and grape juice.

In the experiments with sheep, one group was given rolled barley with table salt (control) and another group received the grain with lithium chloride (treatment). Lithium chloride tastes like salt but causes gastronomic illness.

The sheep that received grain with salt readily ate the feed during the experiment (Figure 1) while those consuming the tainted barley consumed much less of the grain during subsequent days. Sheep in the treatment group continued to sample the barley every day, however, and readily consumed it when they discovered that the feed was no longer mixed with lithium chloride. The sheep readily remembered the experience at least three months after the initial treatment. However, the repeated sampling of feed that was treated presents a problem if animals are to be trained to avoid poisonous plants and other substances.

Our association with livestock research has been rewarding, and the management problems have been interesting and challenging. Behavioral principles or theory provided some guidelines for our research, and the results usually had some ramifications for behavioral theory. This interplay occurred so often that the traditional distinctions between applied and basic science no longer had much relevance for us.

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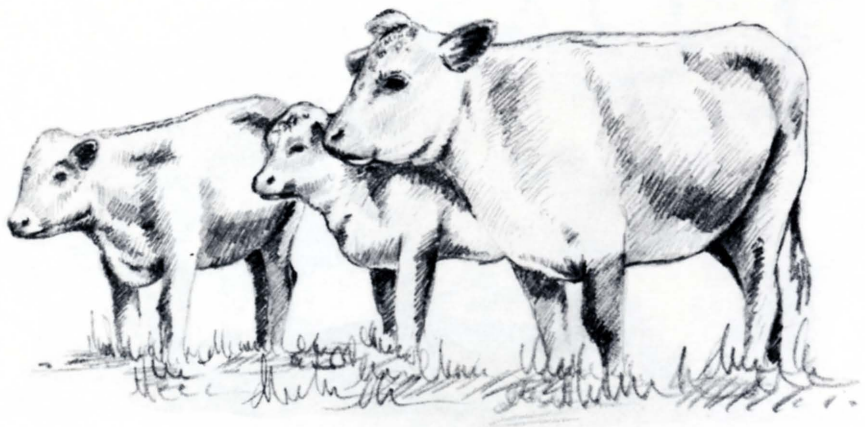
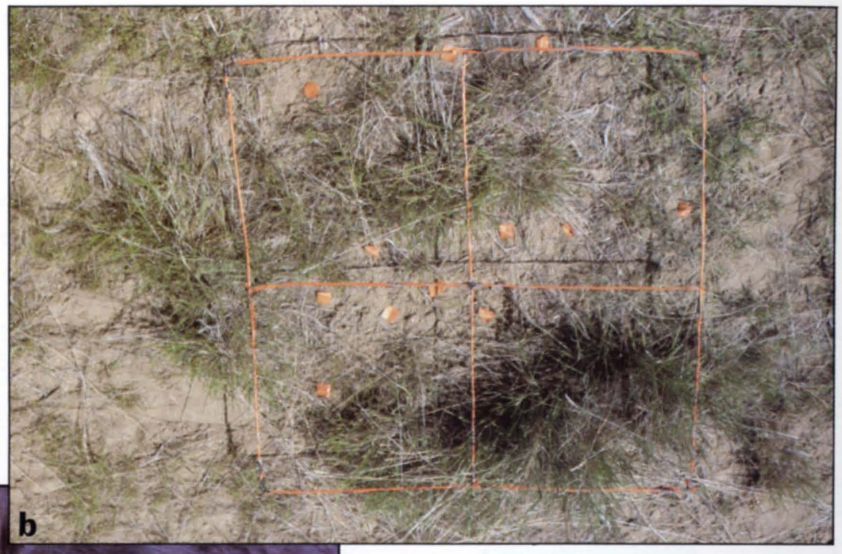
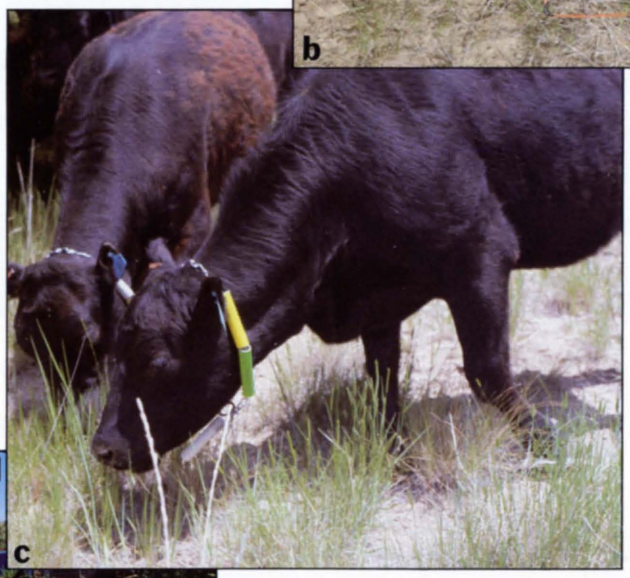
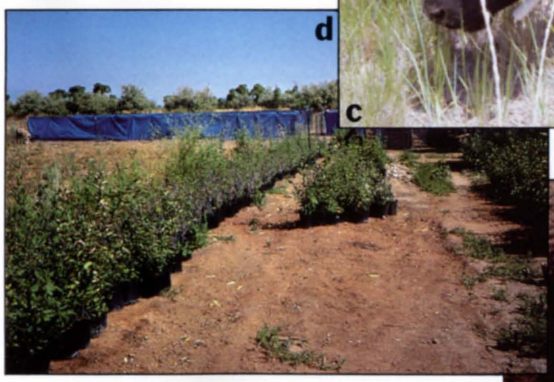








Scientists have several promising leads in their attempts to understand and control livestock behavior. Among the factors studied are systems of grazing management; (a) shows the pasture at Tintic used to study short-duration grazing.

(b) Another study found that cattle avoid tramping on tussocks, a finding which may help assess the merits of short-duration grazing. The red flags indicate the location of hoofprints.

(c) Social facilitation, the desire to be with other animals and mimic their behavior, is an important factor governing animal behavior.

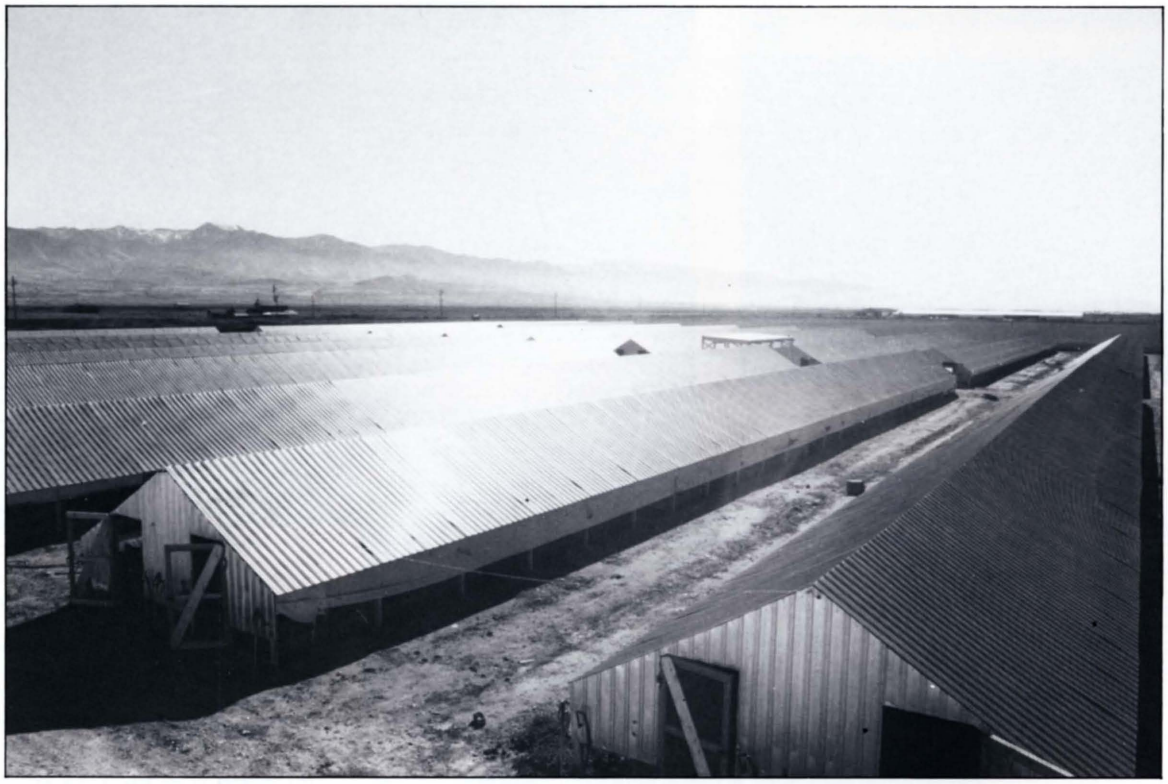
(d) The Green Canyon research facilities. Shown are potted plants used to study the influence of early learning on grazing preferences of sheep.

(e) A lamb and ewe used in the study of social modeling. What a lamb learns while grazing with its mother seems to influence its grazing behavior later in life. Findings may help producers tailor an animal's dietary preferences to available feeds.

PHOTOS: E. FLORES AND D. BALPH

GENETIC PROBLEMS IN MINK CULTURE

L. C. ELLIS and N. C. PACE



Pelts from mink raised in culture are used to make a variety of functional garments. Women desire a high-quality, functional coat, one that will last a lifetime and that can be worn to market, work or social gatherings. A mink coat fills all of these needs. Because mink raised in the United States are of a high quality, many of our pelts are sold overseas where they are processed and marketed.

The natural or wild-type mink is dark brown. Mink farmers in the United States were instrumental in developing a number of mutant color strains of mink. Today there are over 40 distinct genetic color strains of mink. Colors range from white to blue, and from brown to black (1). Farmers in Utah tended to concentrate on developing a strain of dark mink whose near-black short guard hair has a blue sheen, and a dark, dense underfur.

All of the color phases except dark mink have arisen from mutations. The dark mink resulted from intensive inbreeding to achieve the fur color, texture and density sought by processors and consumers. Utah now ranks second in the nation in pelt production with gross sales of about $18 million annually.

The intensive inbreeding necessary to obtain the dark strain of mink resulted in a number of genetic problems. We have studied the following problems concerning infertility, reproduction, and pelt-priming defects in mink (Table 1). These genetic problems have undoubtedly resulted from mutations (spontaneous changes in genes that occur as a result of cosmic radiation, environmental pollutants, food additives, insecticides, etc.). On chromosome six in man and rat, chromosome 17 in the mouse, and on the corresponding chromosome in mink and other animals, there are a series of genes close to the centromere (the point where the astral ray is attached to the chromosome). This series of genes is commonly known as the major histocompatibility complex (MHC), but are also referred to as the HLA, growth, reproduction and production complex of genes.

The MHC genes are responsible for reproductive events including conception, embryonic development, birth defects, lactation, coat color, growth and immunological responses (including susceptibility to disease, such as the susceptibility of the Aleutian strain of mink to Aleutian Disease), diabetes, and susceptibility to cancer. The problems in mink culture that we have studied are in these categories. During gametogenesis (formation of the egg and sperm) one chromosome from the dam and one from the sire cross over to form

two new chromosomes. Since it is difficult for chromosomes to crossover next to the centromere, the whole complex of genes in this area moves to the new chromosome as a unit. As a result, the undesirable traits are co-selected with desirable genes.

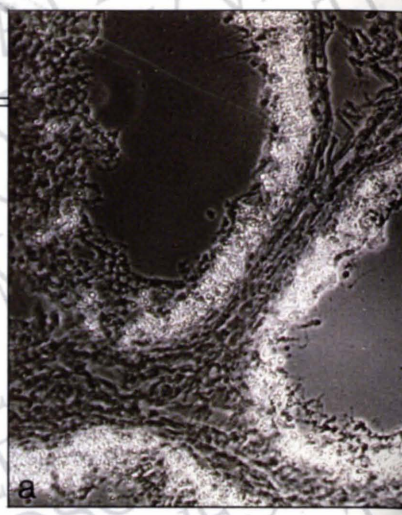
Dwarfism in Hereford cattle was fairly common during the 1950s and 60s. This reproductive problem is an example of a genetically inherited production problem similar to those which occur in mink; traits associated with a blocky body type and rapid weight gain desirable in breeding stock were co-selected with undesirable traits. Dwarfism in Herefords was eliminated from registered breeding stock after it was identified as an inherited trait. Genetic selection lets animal breeders keep desirable traits or eliminate undesirable traits, as long as there is a way to identify which traits are present in the offspring.

A chemical test is one method to identify inherited traits. We are developing such tests for use with mink. Currently, offspring must be visually examined and production records kept to determine whether desirable or undesirable traits have been inherited. However, some traits do not appear for several years. If there is a latent period before the trait is expressed, breeders may assume that the trait has not been inherited. Since most undesirable traits are usually recessive (they require a gene from each parent), they may not be expressed for several generations. The recessive unexpressed genes for the undesirable traits then accumulate in breeding stock until the undesirable trait suddenly becomes obvious. There are several such undesirable traits of concern to mink breeders.

Primary infertility in dark mink is very similar to delayed puberty in man; the testes fail to develop fully and the individual is infertile. This genetic condition also occurs in rodents and is due primarily to a lack of hypothalamic cells that produce gonadotropin releasing hormone (GnRH), a hormone that causes the pituitary to release follicle stimulating hormone and luteinizing hormone required for germinal cell development and the secretion of the masculinizing hormone, testosterone. We have found low levels of luteinizing hormone and testosterone in the dark mink suffering from primary infertility. In mature laboratory animals, fertility has been restored by transplanting fetal hypothalamic cells to the brain. We have injected GnRH into primary infertile mink and, as has been observed in humans, found that some individuals respond well to the treatment while

TABLE 1. Inherited problems related to infertility, reproduction and pelt priming defects in dark mink.

I. Infertility and reproduction	
A. Male	
1. Primary infertility (delayed puberty)	A lack of hypothalamus GnRH Hormone secretion due to cell death in brain or other complications of pituitary and/or testes.
2. Secondary infertility	
a. Autoimmune orchitis	Histamine-induced breakdown of the blood-testicular barrier and the subsequent attack of the germinal cells by the immune system.
b. Cytotoxic destruction of testes and epididymis	Spontaneous cellular self of testes and epididymis destruction of unknown origin.
3. Genetic infertility	Genetic abnormalities of either conceptus, sperm-ovum interaction or embryo development where all females bred by a male fail to produce any offspring.
4. Cryptorchidism	Adhesions of the inguinal fat pad to the inner scrotal sac preventing migration of the testes into the scrotal position.
B. Female	
1. Neonatal kit loss	
a. Normal appearing	Kits are either born dead or die within 48 hours of birth due to spontaneous cytotoxic lesions. High ambient temperature increases losses.
b. Watery kits	Massive edema and large size results in difficult delivery. Kits are usually stillborn.
2. Nursing sickness	The animals go off feed, lose weight and develop a black tarry stool and die. It occurs during late lactation or shortly after weaning.
II. Male or Female	
A. Non-reproductive seasonal losses of mature mink	Appears to be stress-related, occurring either during breeding or fall molt.
III. Pelt priming defects	
A. Singe	Abnormalities of hair follicle structure causing the hair to take on an uncharacteristic shape.
B. Cotton fur syndrome in dark kits	Appears to result from iron deficiency either in milk or due to inefficient absorption in the kit.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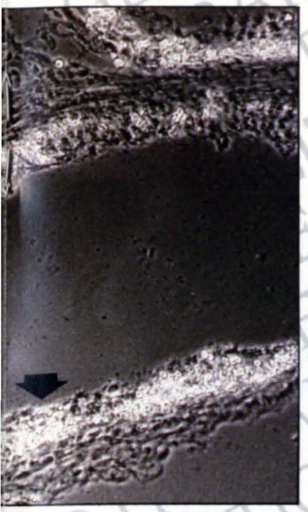


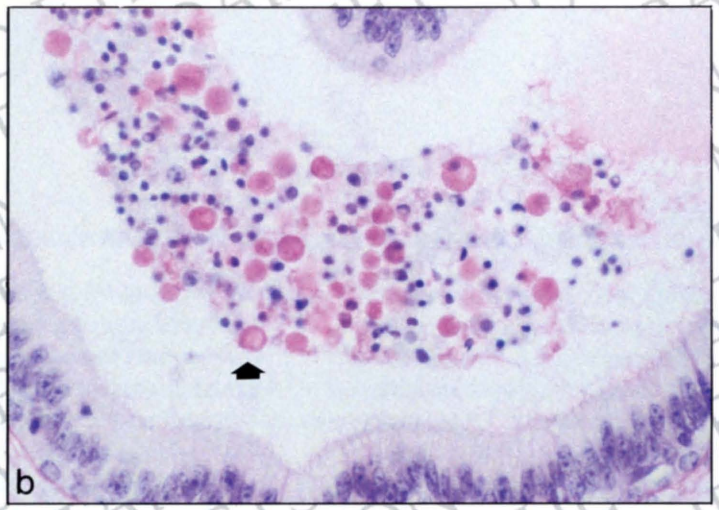
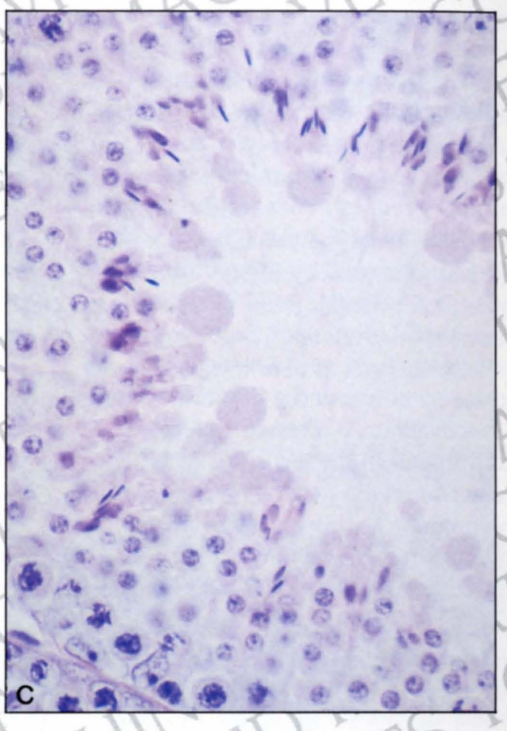
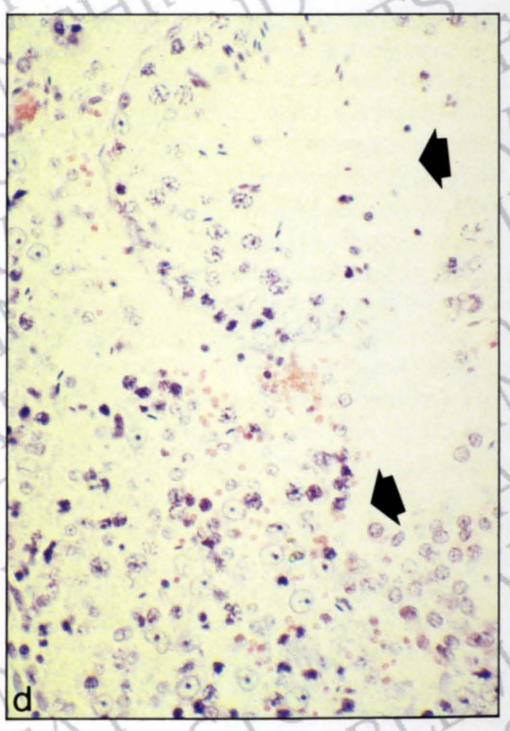


FIGURE 1. Photomicrographs of dark mink testes and epididymides showing early cytochemical lesions. (a) Phase contrast microscopy showing cytochemical autodestruction of epididymal tubular lining of dark mink. (b) Normal-appearing epididymal tubule containing acidophilic "puff ball" from cells undergoing cytochemical autodestruction elsewhere in the organ. (c) Normal-appearing section of testes from dark mink. (d) Seminiferous tubules almost completely destroyed by cytochemical autodestruction of the germinal and tubular cell walls.





others do not. Results suggest that these non-responders may be suffering from defects of either the pituitary gland or testes, or both organs, defects that would limit the effectiveness of GnRH.

Secondary infertility of the autoimmune type can occur in infertile humans in either males (especially after a vasectomy) or females. This type of infertility is caused by the production of antibodies against sperm. We have found that dark male mink have an abnormally high rate of testicular histamine synthesis and a diminished rate of inactivation. As a result, histamine accumulates in the testis (2). Histamine breaks down the normal barrier (3) that prevents the immune system from attacking mature germinal cells. The sperm antigens then pass out of the seminiferous tubules into the interstitial space. Lymphocytes can then become activated and start to produce antibodies against the germinal cells and the testes. While all strains of mink have some antisperm antibodies, only the dark mink become infertile, which indicates that there is a basic difference in the immune system of this strain.

Some animals develop interstitial cell orchitis, which destroys the ability of the gonad to reproduce androgens. Others develop autoimmune complexes around the seminiferous tubules, which alter sperm development. Anti-sperm antibodies have been found in all strains of mink studied, both male and female (those previously bred and whelped), but only the dark males exhibited the autoimmune orchitis. This suggests that the immune system of dark male mink differs from that of other mink.

In some affected animals, the germinal epithelium inside the seminiferous tubules is destroyed (4). This latter condition has recently been identified in a man (Tung, personal communication) who had two children, but was unable to have additional children. He had experienced testicular pain and regression. Testicular biopsy revealed extensive spontaneous autoimmune orchitis similar to that found in mink.

Self-destruction of dark mink testes and their epididymides occurs spontaneously in dark mink. Testes of these animals may be of normal size and affected males can sometimes successfully breed if the condition is unilateral. If the ailment affects both sides, the male will be infertile. Infertility is caused by the degeneration of the tubules that conduct sperm through the epididymis (Figure 1). This degeneration lets sperm leak out into the interstitial area, where leukotoxins are released causing neutrophils, and macrophages to migrate into the area to digest and remove the foreign cells. A sperm granuloma is then formed that allows only some dead, headless or tailless sperm to pass into the ejaculate during copulation.

We do not know what causes spontaneous degeneration of testicular cells and the epididymal cells, but when we induced early testicular maturation by treatment with melatonin, all strains experienced these degenerative changes (5). The more inbred the strain of mink, the more severe the degeneration of the testes and epididymis; there was even some total cellular destruction of these two organs (Figure 2). We have also observed this condition spontaneously in wild deer and in a Simmental bull (unpublished data). However, there have been no reports of this condition in man. Results indicate the risks of treating potential breeding stock with melatonin.

Genetic infertility is characterized by infertility of every female bred to a certain male. Since polyandry (i.e., the breeding of a female to more than one male) is a common practice in mink culture, this condition may not be apparent. This condition has been found in most of the species studied, including man.

Cryptorchidism. Mink differ from many other species in that the tunica vaginalis (the pathway of the testes from the abdomen to the scrotal sac) originates higher on the abdomen and does not pass through the pelvis. Instead, it passes through an inguinal fat pad between the skin and the body wall in the pelvic area. If the fat pad enlarges, the adipose cells adhere to the tunica vaginalis and prevent the testes in the tunica from migrating into the scrotal sac (Figure 3). Some farmers have manually forced the testes into the scrotal cavity, and a "snapping" occurs as the adhesions of the fat to the tunica vaginalis break. While we found adhesions in all strains of mink, the incidence of retained testes at breeding is much higher in dark mink (6). Retained testes are covered with 1/4 to 5/8 inch of fat. Restricting the feed intake during December and early January to reduce the size of the fat pad resulted in normal testicular descent into the scrotal sac. It appears that the fat cells in this pad normally respond to androgens to allow normal testicular-tunica descent. The dark strain has lower testosterone levels than the other strains of mink (7), which may account for the higher incidence of this condition in dark mink.

Neonatal kit loss is exceptionally high in dark mink. Mortality increases as environmental temperature increases and is also directly related to pelt quality. The ailment is a genetic trait. Crossing a low-kit-producing strain with a high-producing strain of dark mink results in progeny whose kit production is intermediate to the two strains (6). Similarly, a wild-type (demi) strain of mink, which was developed by crossing the animals four to five times with the dark strain, also exhibited excessive kit loss. Recent observations indicate that there is extensive cell death in many organs, including the heart, brain, intestine and skeletal muscle. Abnormal pancreatic function [i.e., decreased insulin, glucagon and somatostatin secretion (8)] has been observed in these kits as well as an abnormal increase in the processing of beta-

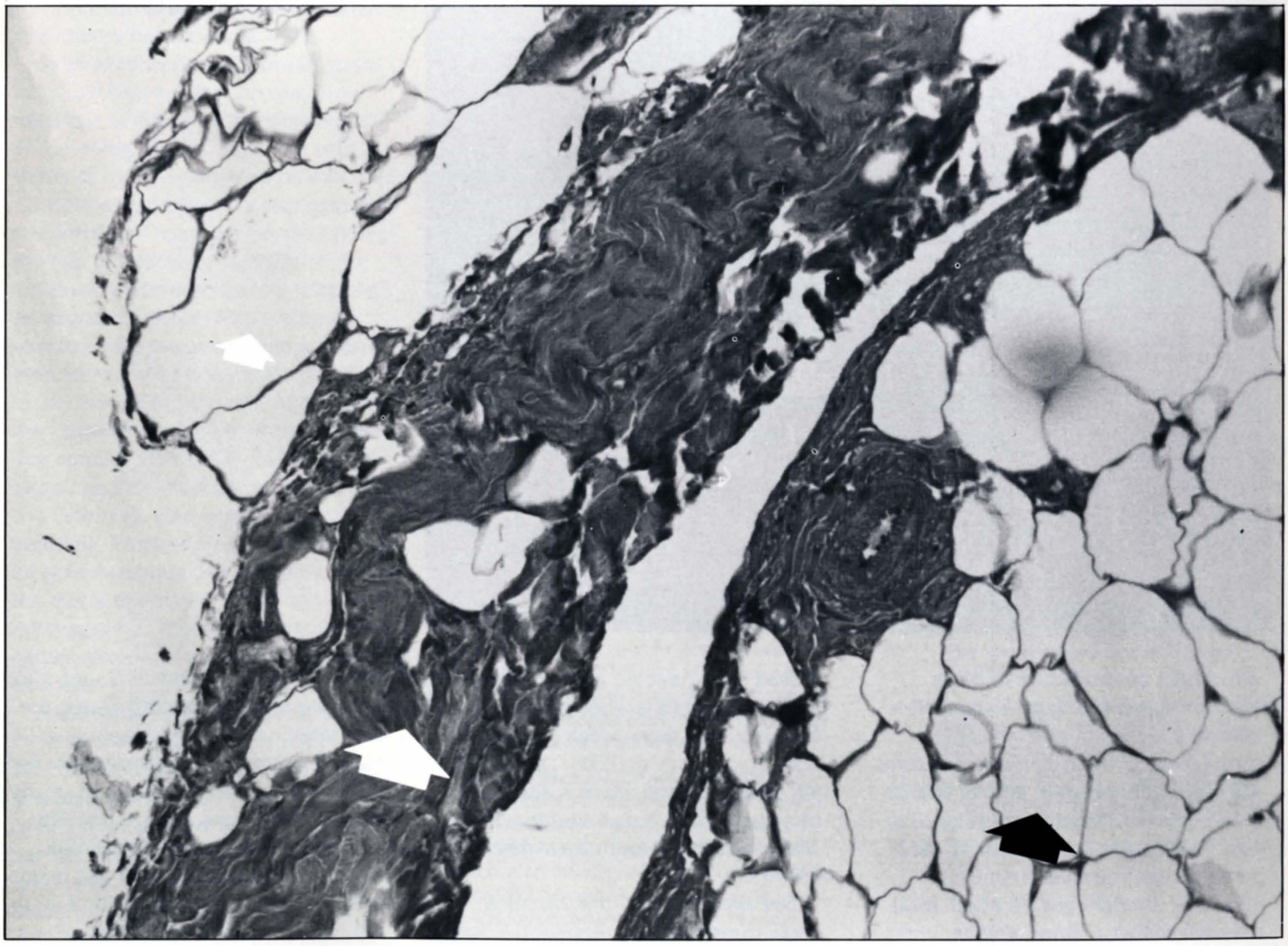
lipotropin to beta-endorphin (9), a compound with morphine activity. Kits under the influence of this morphine-like compound care little about eating, and pancreatic secretion is impaired.

Watery kits is a form of neonatal kit loss due to abnormal cardiovascular function. The ailment causes extensive edema and large body size. We found the hearts of affected animals to be small with valvular damage and fibrotic lesions. Heart failure in these kits results in low blood pressure and the subsequent massive edema. Average hearts of normal kits weigh 0.140 g (range 0.127 to 0.149 g) while those from watery kits weight 0.117 g (range 0.038 to 0.173 g).

Nursing sickness occurs towards the end of the lactation period when dams are unable to obtain enough energy and nutrition from feed. The dams stop eating, lose weight, and soon die. They develop tarry stools due to blood loss into their intestines. Histologic evaluation of their organs showed extensive loss of the mucosal cells lining of the tips of the villi. Death results from dehydration and cellular losses of major organs (heart, brain, etc.) similar to the cellular destruction observed in the testes and epididymis of secondary infertile dark mink and in neonatal watery moribund and dead kits.

Female infertility occurs in a small number of females in any population, but the incidence is higher among first-year dark mink. Affected female mink fail to breed even following injection

FIGURE 2. Photomicrograph of a dark mink testis (right) and epididymis (left) of a dark mink implanted with melatonin. Note the total loss of cells of the testis (the black arrow shows only the basement membrane of the seminiferous tubules where the germinal and interstitial cells are missing) and epididymis (the small white arrow shows the loss of epididymal cells while the large white arrow shows an area of fibrosis also found in some testes).



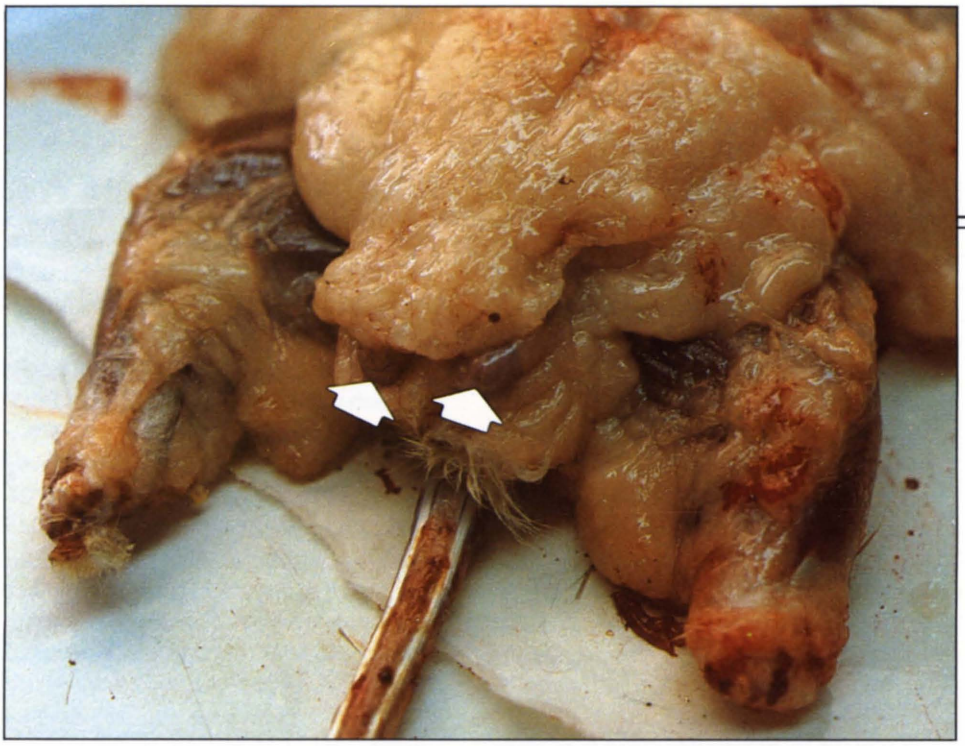


FIGURE 3. Pelvic region of a pastel mink showing the two testes imbedded in the inguinal fat pad (arrows). The fat pad has been dissected from the testes.

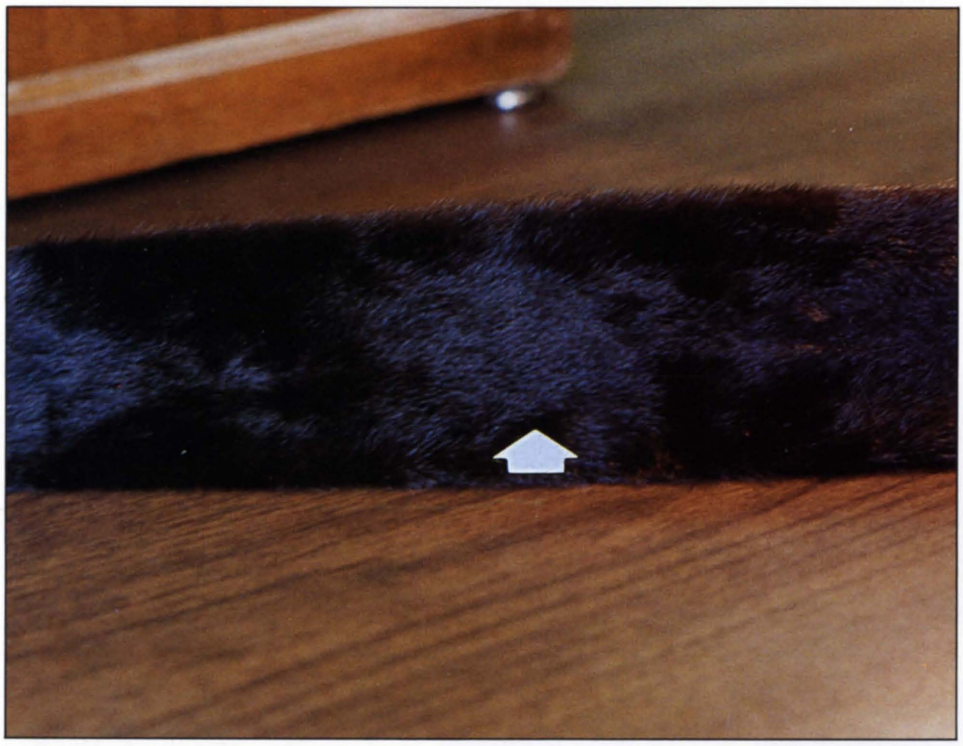


FIGURE 4. A dark mink pelt with singe, the light "metallic" areas surrounded by darker normal fur.

with GnRH and exposure to fertile breeder males. Histologic evaluation indicated a general lack of ovarian stimulation, an indication that problems with either the pituitary and/or ovaries individuals (i.e. females which failed to gain weight after lactation, runts, etc.). Some animals develop a condition known as "straight gut" in which fecal material contains almost entirely unprocessed feed. Affected animals die during the fall months when farmers withhold feed one day a week to get mink into fur-priming condition. During the fall pelage change, there is also an increased incidence of "sudden death" prevent animals from responding to the treatment.

Seasonal losses of mature mink occur during periods of stress (i.e. spring breeding and fall pelage change). Male losses during the breeding season are comparable to female losses due to nursing sickness, an indication that both ailments could be caused by the same factor(s). Fall losses include unthrifty among apparently healthy animals. "Sudden death" in humans has been described as a response to stress, and the mink may serve as an animal

model for this ailment.

In summary, it now appears that the dark mink is susceptible to tissue degeneration in the gonads or brain (causing infertility), or in other tissue (causing neonatal kit loss with or without edema). In mature mink, this tissue degeneration is associated with nursing sickness and seasonal stress. There have been reports of similar ailments in humans. For example, women's ovaries suddenly ceased to function after a pregnancy or other conditions such as galactosemia. There are also forms of colitis with destruction of mucosal and liver cells. Moreover, the ailment can be associated with bleeding as observed in mink. In one case, the ailment was induced by heat stress at work.

Singe is caused by abnormal guard hairs (10) that result in an abnormal reflection of light on dark pelts (Figure 4). Breeding studies show that some forms of this condition can be inherited. Abnormal hair follicles or enlarged cells and increased numbers of cells within the hair follicle exert pressure on the developing hair and cause it to take on an abnormal shape. As a result, the affected hairs are in a different position than surrounding hairs and reflect light in an unusual fashion (11). Males with the condition pass it on to their progeny. The condition is hard to trace because singe may not show up until mink are 3-4 years old, after several years of breeding. Thus, carriers of the trait may be pelted (replaced as breeders) before the trait is expressed. When the trait is expressed by progeny, environmental causes rather than genetics may be blamed.

Cotton fur syndrome appears towards the end of lactation in dark kits (12). The lower portion of the guard hairs and underfur are non-pigmented. The color intensifies soon after kits start to eat solid feed and the condition is less noticeable. The animals also have a microcytic anemia indicative of iron deficiency, a condition which could be due to a lack of iron in the milk as a result of marginal iron absorption in the intestine by the dams. Some kits of a litter have more cotton fur than others, an indication that kits differ in their ability to absorb iron from the gut. Some mink never obtain a full, dark-colored pelage even after the fall molt, perhaps due to a genetic impairment of iron absorption.

Conclusion

Many of the problems discussed above are common to mink, humans, and other animals. Mink are an ideal animal for the study of inherited problems. Thousands of animals are bred annually on many farms, so inheritance of ailments can be traced quickly and there are adequate numbers of afflicted animals to study. Mink mature quickly and can be bred/pelted in less than one year. Mink also apparently have a high incidence of spontaneous mutations of economic significance, and intensive inbreeding has increased the frequency of defective genes. Knowledge of these ailments in mink is useful in alleviating these conditions in other species.

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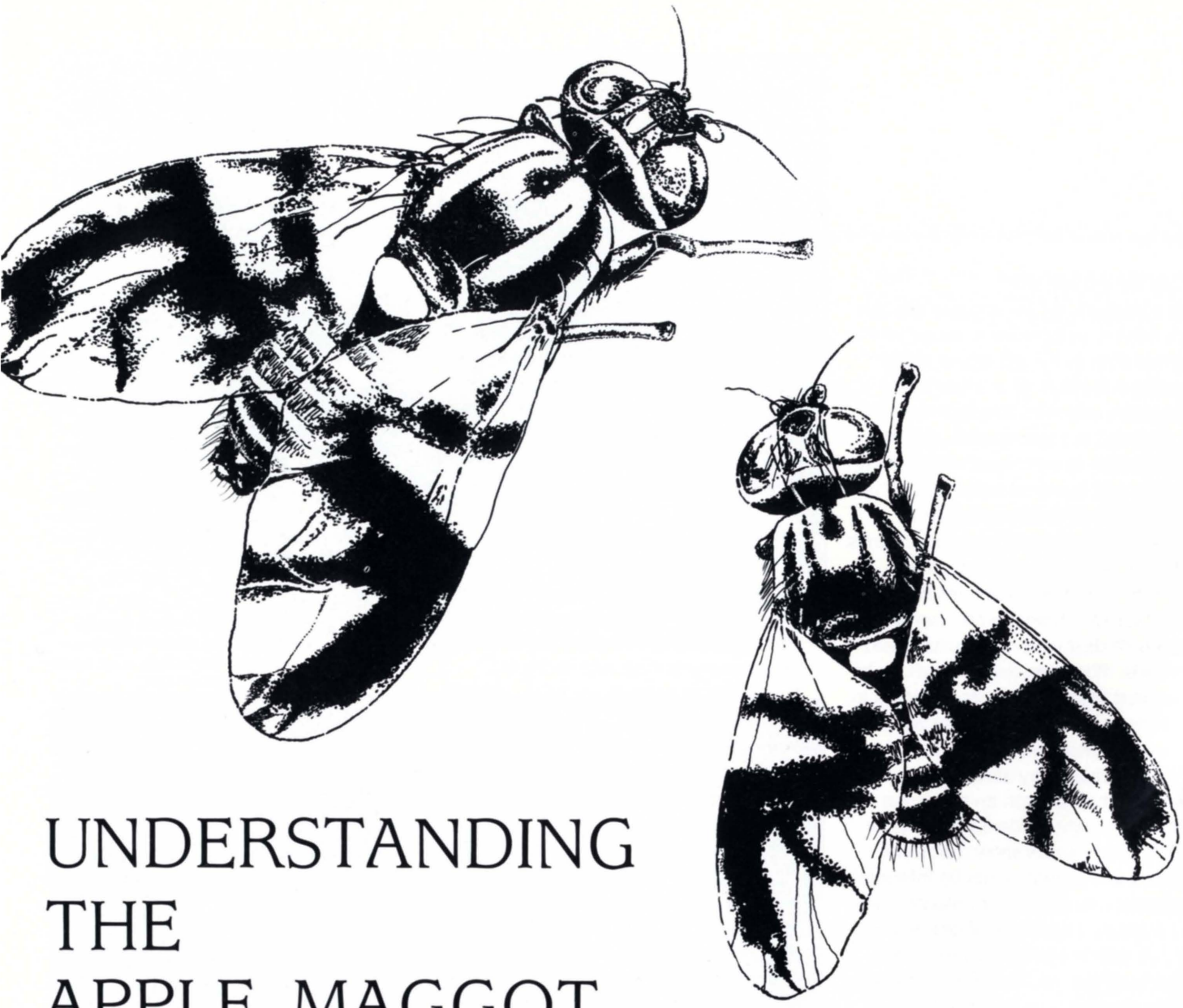


UNDERSTANDING THE APPLE MAGGOT

D. W. DAVIS and V. P. JONES

The apple maggot, *Rhagoletis pomonella* WALSH, was found attacking cherries near Mapleton in Utah County in 1983. The discovery of this pest and of the western cherry fruit fly, *Rhagoletis indifferens* CURRAN, in 1980 modified the pest complex on Utah cherries. Previously, the most common insect and mite pests of concern to cherry growers were the black cherry aphid, cherry slug, and spider mites.

Adult apple maggots and western cherry fruit flies insert eggs into the fruit. After several days, the eggs hatch and larvae burrow throughout the fruit. Larval development is completed in about two weeks. Larvae then bore out of the fruit and pupate in the soil. Most flies emerge the following spring, but some may require two or more years before emerging.

To comply with interstate marketing rules, apple growers whose orchards are within 1/2 mile of a location where any apple maggots have been caught must follow a strict pesticide-treatment program. Treatments include high doses of insecticides applied at bi-monthly intervals, regardless of whether flies are found in the orchard. Treatments must begin when the first fly is detected and continue until just prior to harvest. These requirements mean that as many as four additional pesticide applications may be necessary. Obviously, such regu-

lations create havoc with pest management programs and greatly increase production costs.

Cherry and apple producers need to economically control these new insect pests utilizing programs that are consistent with the principles of integrated pest management (IPM). Development of such a program of control requires accurate information on the effectiveness of insecticides, distribution, host range, and phenology (development in relation to temperature and season) of the insects, monitoring techniques, and how control practices will affect other insects and mites in orchards.

Previous research concerning the apple maggot conducted elsewhere was of little value to growers in Utah; apple maggots in Utah attack cherries and hawthorns, not apples (and hawthorns) as in most apple-growing regions in the eastern United States. For those reasons, an extensive research program was developed to learn more about the insect and help Utah growers control the insect. The research project was funded by the Utah Agricultural Experiment Station, the USU Cooperative Extension Service, the Utah Department of Agriculture, and the California Department of Food and Agriculture. This report concerns some of the preliminary findings of the research project.

Host and Geographical Range in Utah

It was necessary to learn the host range and geographical distribution of the Utah strain of apple maggot in order to determine the extent of the problem and the feasibility of eradication.

The distribution of the apple maggot was originally thought to be restricted to the Mapleton bench (on cherries) and a portion of Cache Valley (on unknown hosts). If it had only a limited distribution in the state, it might have been possible to eradicate the pest by removing host plants. However, a 1985 survey of the state by Wilford Hanson, USU entomologist, and Clive Jorgensen, entomologist with Brigham Young University and the USU Extension Service, showed that the apple maggot was widely distributed and often quite abundant where hawthorns or cherries were found (Figure 1). The only major Utah fruit-production area not infested by apple maggot was in Washington County. Results clearly indicated that it was not feasible to eradicate the pest.

Many plants were examined that were potential apple maggot hosts. Fruit fly larvae were found in relatively few of the many kinds of fruits and berries that we dissected and examined. Any suspected host plants were sampled and brought to the laboratory where some were dissected. If any larvae were found, they were held until adults developed and could be identified. Suspected hosts included any fruit botanically

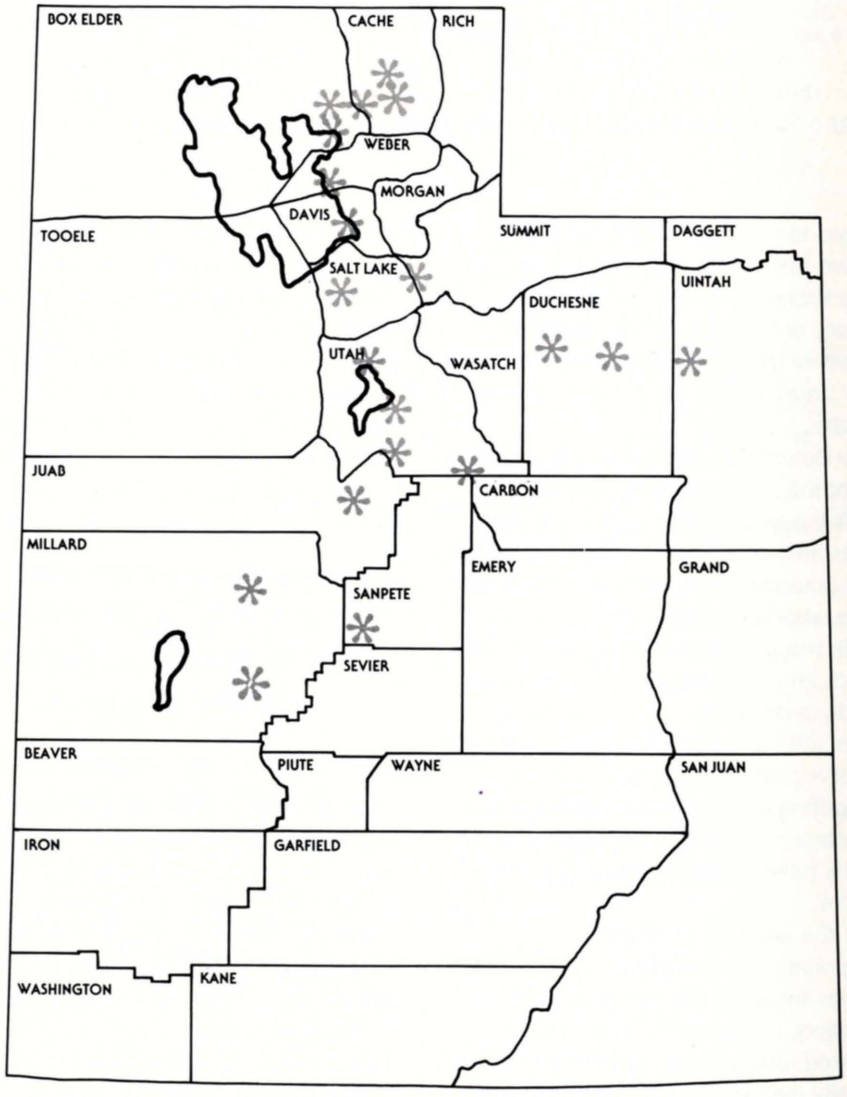


FIGURE 1. Utah locations where apple maggots have been trapped.

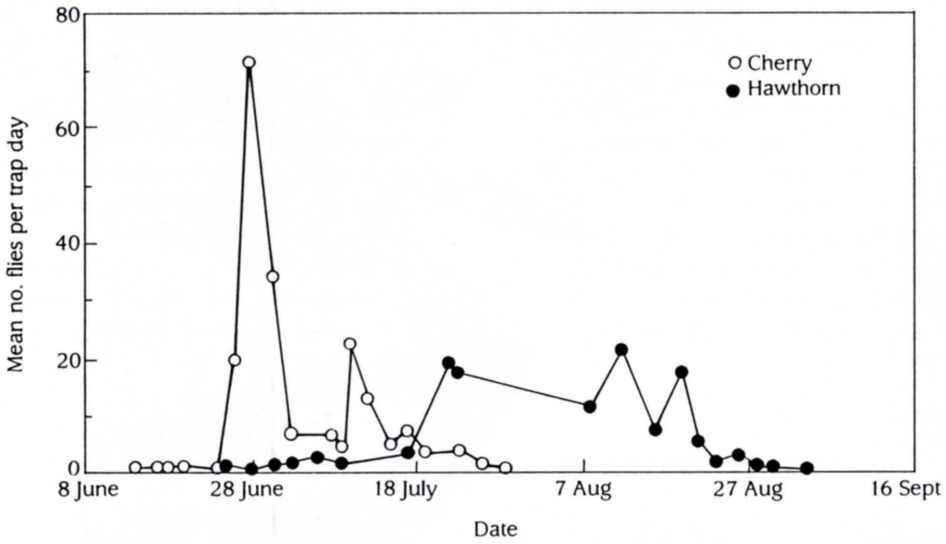


FIGURE 2. Seasonal phenology of apple maggots on two different hosts in Utah County (1985).

related to or similar in appearance to known hosts. Also examined were any fruits known to be hosts of related species of fruit flies and all fruits and berries occurring in substantial numbers near areas where adult flies had been caught.

To determine whether apple maggots might infest apples, large numbers of adult maggots were placed in sleeve cages around apples on trees. All available potential hosts were also placed in large laboratory cages with many adult apple maggots. Apple maggots did not attack any apples in the experiments conducted during 1985. However, in 1986, USU entomologist Frank Messina observed apple maggots apparently depositing eggs in unripe apples under laboratory conditions. No apple maggot adults have yet been reared from these apples.

In the field, up to 90 percent of unsprayed tart cherries and native hawthorns are often infested with apple maggots. Sweet cherries are also infested, but harvest of sweet cherries is usually over before the period of peak apple maggot flight. Infestation of fruit on trees with unpicked sweet cherries is comparable to tart cherries. Few maggots have been found in sprayed cherry orchards, an indication the pesticide treatments are effective if properly timed. Under field conditions, it is not possible to distinguish between cherries infested with apple maggots and those infested with western cherry fruit flies.

Results indicate that the strain of apple maggot found in Utah is not yet adapted to apples.

In addition to cherries and native hawthorns, apple maggot larvae were found in ornamental hawthorns, one unidentified variety of crabapple, *Pyracantha*, plums from volunteer rootstock, and apricots. There were only low levels of infestation in the last three hosts.

No apple maggot larvae have been found in any commercial or backyard apples in Utah. Adult flies may be trapped in apple trees, but no larvae have been found in thousands of commercial apples checked by inspectors with the Utah Department of Agriculture nor have any been found in "high-risk" fruit (unsprayed backyard fruit or fruit near infested cherry and hawthorn trees). Results indicate that our strain of apple maggot is not yet adapted to apples. However, intensive surveying and monitoring must continue to minimize the risks associated with possible adaptation.

Integrated Pest Management

Integrated pest management considers how pesticides will affect the entire complex of pests, the natural enemies of the target insect, and the direct and indirect effects of management techniques on the plant itself.

Accurate trapping data are essential in these and related studies. Studies in 1985 indicated that apple maggots in Utah were not readily attracted to the types of traps utilized in the eastern United States. In 1986, it was found that adding a bait composed of apple volatiles, which increases trap catches in the East, actually decreased catches under Utah conditions. Although the yellow, sticky cards now used to monitor populations are fairly efficient, adding a packet of ammonium carbonate greatly increased trap sensitivity. Experiments are now underway to determine how best to add ammonium carbonate baits to the cards for commercial use.

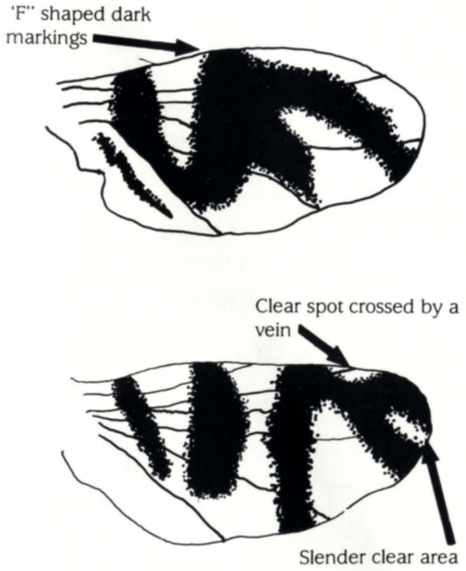
Temperature and Fruit Fly Activity

Optimal timing can make an insecticide more effective against pests and reduce its negative effects on beneficial insects and mites. Data collected during 1985 and 1986 are being used to program a computer model that predicts insect development. The model considers the fact that, within limits, the higher the temperature, the faster an insect devel-

ops. By monitoring maximum and minimum temperature, growers will then be able to use the model to predict when insects will emerge. Two weather stations, one at Mapleton and one at Spanish Fork, were established in 1985 in order to collect more-accurate weather data. Weather was also monitored in Box Elder and Cache counties during 1985. In 1986, four weather stations were established in Utah County, two were established in Cache County, and one was established in Box Elder County.

The western cherry fruit fly will not develop at temperatures below 41° F while USU research, based on data from the eastern U.S., indicates that 47° F is the lower threshold for apple maggot development. As shown in Figure 2, apple maggots associated with cherry trees developed sooner than those associated with hawthorns, but emergence tends to overlap somewhat. During 1985, the maximum average peak catch in hawthorns occurred approximately six weeks after the peak catch in cherries. However, peak catch in hawthorns was only about 10 days later during 1986. Using the 47° F threshold (which means that degree days do not accumulate as quickly as with the western cherry fruit fly, whose threshold temperature is 41° F), the first apple maggots were caught at 490 degree dats (DD) in 1985 and at 546 DD in 1986. Degree days are measurements of heat units. One DD accumulates when the average temperature is one degree above the lower threshold for 24 hours.

During the past four years, the western cherry fruit flies have started their activity and reached peak levels in a cycle that occurred 2-3 weeks earlier than that of the apple maggot in cherries. Based on the threshold temperature of 41° F, the first activity occurred at about 873 DD. The developmental model for western cherry fruit fly developed in Oregon seems to adequately predict the development of the western cherry fruit fly in Utah.



The characteristic "F" shaped dark markings of the wing of the apple maggot (above) distinguish it from the western cherry fruit fly (below).

Impact of Pesticides for Apple Maggot on Other Pests

The high reproductive rate and short generation time of mites mean that they are a sensitive indicator of any pesticide-induced upsets. During 1986, we studied the pesticides Zolone®, Imidan®, Guthion®, and Lorsban® (registration of Lorsban® for cherry is pending). We found Zolone® had the least effect on mite predators at the rates required by quarantine. All materials provided adequate control of apple maggots. However, the high rate of Guthion® required by quarantine actually increased spider mite levels by 12-fold at one month following application compared to trees sprayed with water only.

Laboratory studies now underway are testing the sub-lethal effects of these pesticides on mite reproduction and survival. The results of these studies will guide pesticide recommendations on both cherries and apples.

Conclusions

The apple maggot and the western cherry fruit fly are new pests to Utah fruit growers. The information provided by this research will help growers effectively control these pests. If present regulations are relaxed so treatment can be based on monitoring information, findings from this research will improve management practices, substantially reduce production costs, and give Utah fruit growers unhampered access to interstate markets.

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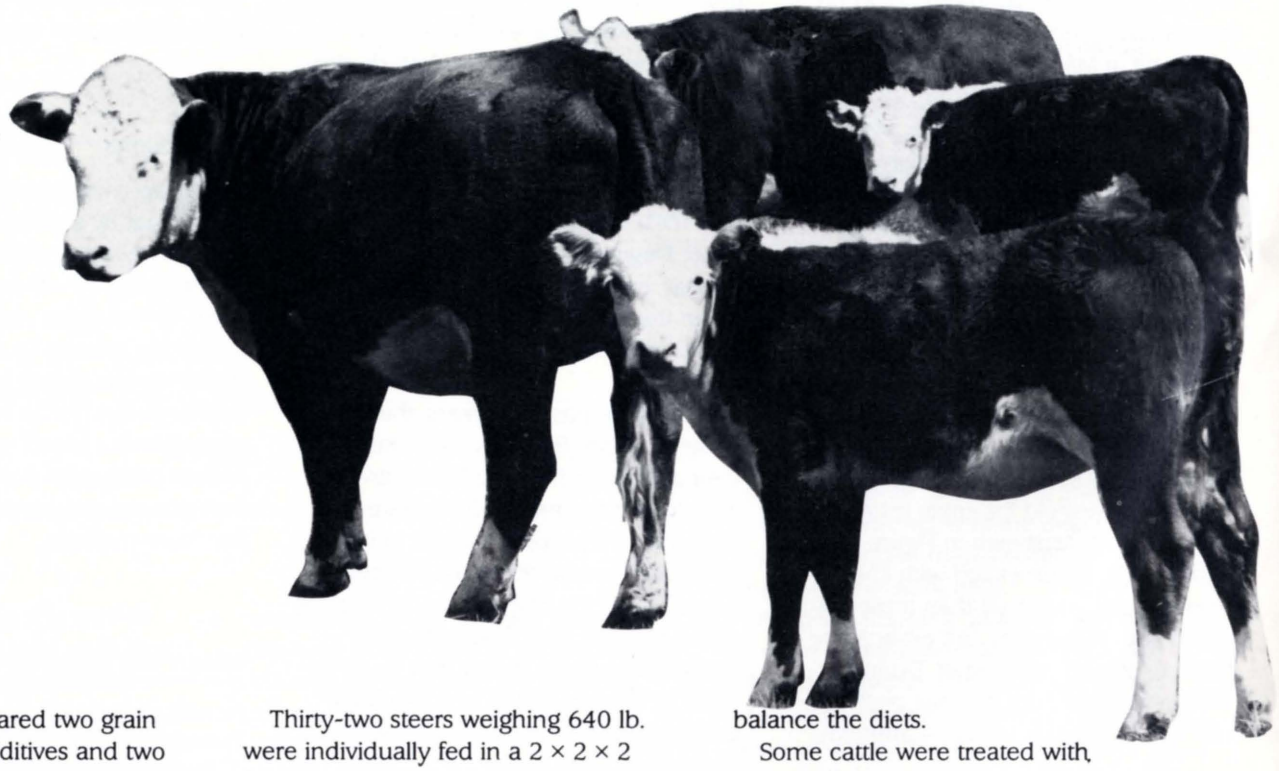
Vincent P. Jones is assistant professor of biology and extension specialist. His research is primarily in the area of IPM of insects on deciduous fruits.

GRAIN, FEED ADDITIVES AND PARASITE CONTROL IN BEEF CATTLE GROWING-FINISHING DIETS

N. J. STENQUIST



A feeding trial compared two grain diets, two feed additives and two methods of internal and external parasite control. The major objectives of this experiment were to:

1. Compare rolled barley to ground corn as an energy source.

2. Compare Monensin (Rumensin™) with Lasalocid (Bovatec®) as a feed additive for growing finishing beef cattle.

3. Compare Tiguvon® to Invermectin® for control of internal and external parasites in growing-finishing beef cattle.

Thirty-two steers weighing 640 lb. were individually fed in a 2 × 2 × 2 factorial experiment. Feed intake, rate of gain, feed efficiency, cost of gain, and carcass characteristics were determined.

The diets consisted of corn silage, alfalfa hay, and either rolled barley or ground corn as the energy source. The feed additives Rumensin or Bovatec were fed at 200 mg/head per day level as a part of a 32 percent protein supplement. The supplement provided the necessary minerals and vitamins to balance the diets.

Some cattle were treated with Tiguvon for internal and external parasites at the beginning of the experiment. This product, a 20 percent concentrate in a ready-to-use solution, was applied at the rate of 4 ml/300 lb. of body weight. The other product, Ivermectin, was injected intramuscularly at a rate of 1 ml/110 lbs. of body weight.

All cattle were implanted at the beginning of the experiment with a Compudose® implant.

Cattle were randomly assigned to each of the treatments.

TABLE 1. Weight gain per day.

Treatment	Gain (lb.)
Rumensin	2.35[a]
Bovatec	2.15[b]
Tiguvon	2.15[b]
Ivermectin	2.35[a]
Rolled barley	2.36[a]
Ground corn	2.13[b]

[a,b]Means with different superscripts differ (P < .05).

TABLE 2. Weight gain per day (two-way factorial means).

Treatments	Gain (lb.)
Rumensin-Tiguvon	2.19
Rumensin-Ivermectin	2.49
Bovatec-Tiguvon	2.11
Bovatec-Ivermectin	2.20
Rumensin-Rolled barley	2.49
Rumensin-Ground corn	2.19
Bovatec-Rolled barley	2.23
Bovatec-Ground corn	2.08

TABLE 3. Total weight gain.

Treatment	Gain (lb.)
Rumensin	458[a]
Bovatec	420[b]
Tiguvon	418[b]
Ivermectin	457[a]
Rolled barley	460[a]
Ground corn	416[b]

[a,b]Means with different superscripts differ (P < .05).

TABLE 4. Total weight gain (two-way factorial means).

Treatments	Gain (lb.)
Rumensin-Tiguvon	427
Rumensin-Ivermectin	485
Bovatec-Tiguvon	411
Bovatec-Ivermectin	429
Rumensin-Rolled barley	485
Rumensin-Ground corn	427
Bovatec-Rolled barley	434
Bovatec-Ground corn	405

All of the products used in this trial are currently available and cleared for use in feedlot cattle.

Weight Gain Per Day

The cattle receiving Rumensin (Table 1) gained 2.35 lb. per day. Those receiving Bovatec gained 2.15 lb. per day. This increase of .20 lb. per day was significant at the .05 level.

The cattle injected with Ivermectin gained significantly more weight per day (2.35 lb.) than those treated with Tiguvon (2.15 lb.). Cattle fed rolled barley gained 2.36 lb. per day while those fed ground corn gained 2.13 lb. per day. This difference of .23 lb. per day was statistically significant. The ground corn used in this experiment was not fully mature and had been mechanically dried. These factors partially explain the differences in performance between diets containing rolled barley and ground corn.

As shown in Table 2, weight gain per day of steers on the Rumensin-rolled barley combination exceeded that of steers fed all other feed-additive/energy source combinations studied. None of the differences were statistically significant, however.

Total Weight Gain

Cattle receiving Rumensin gained significantly more total weight (458 lb.) over the 195-day feeding period than cattle receiving Bovatec (420 lb.) (Table 3). Cattle receiving Ivermectin gained significantly more weight than those receiving Tiguvon. If live cattle sold for $55/cwt., treatment with Ivermectin would increase returns by $19.80. Ivermectin cost approximately $3.50 per head while treatment with Tiguvon cost $.36 per head.

Cattle receiving rolled barley gained 460 lb. while those receiving the ground corn gained 416 lb. This difference of 44 lb. was significant at the .05 level.

As shown in Table 4, steers on the Rumensin-Ivermectin combination outperformed all other feed-additive/energy source combinations studied in total weight gain.

TABLE 5. Feed efficiency.

Treatment	DM (lb.)/ Gain (lb.)
Rumensin	7.50
Bovatec	8.11
Tiguvon	8.18
Ivermectin	7.48
Rolled barley	7.44
Ground corn	8.17

Feed Intake

The cattle in this experiment consumed an average of 17.29 lb. of dry matter per day. There was little difference in intake between the various treatments.

Feed Efficiency

Cattle receiving the Rumensin required less dry matter per lb. of gain than those receiving Bovatec, (Table 5). Cattle fed rolled barley required less dry matter per lb. of gain than cattle fed ground corn. The cattle receiving Ivermectin were also more efficient than those threated with Tiguvon. However, none of these differences was statistically significant.

Carcass Information

There was little difference in any of the measured carcass traits. Hot carcass weight, marbling score, percent heart kidney and pelvic fat, rib eye area, and grade were all similar. Fat thickness for cattle receiving the Ivermectin was slightly greater, an increase which reflects the increase in gain per day and total weight gain referred to above.

Conclusions

The following conclusions can be drawn from this experiment:

1. Rolled barley was superior to ground corn in daily gain (2.36 lb. vs 2.13 lb.) and feed efficiency (7.44 lb. vs 8.17 lb.).

2. Rumensin was superior to Bovatec in daily gain (2.35 lb. vs 2.15 lb.) and in feed efficiency (7.50 lb. vs 8.11 lb: of dry matter).

3. Ivermectin injected cattle gained 2.35 lb. per day while those receiving Tiguvon gained 2.15 lb. The cattle receiving Ivermectin required 7.48 lb. of dry matter per lb. of gain while those receiving Tiguvon required 8.18 lb. of dry matter.

4. There were only slight differences in carcass characteristics between cattle on different treatments.

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CHEMOTHERAPY OF VETERINARY VIRAL DISEASES

R. W. SIDWELL

Animals, as humans, are afflicted with serious virus infections. These infections can cause substantial mortality and decrease productivity. Vaccines can control certain virus diseases of livestock, but many other viruses can be controlled only by quarantine, disinfection, or, if the infection is serious, slaughter of infected or exposed animals. Antiviral chemotherapy, the use of virus-inhibiting drugs, is an alternative which has become particularly attractive. The use of antiviral drugs in the treatment of human virus diseases demonstrates that this approach is feasible and realistic.

A livestock virus disease suitable for treatment with antiviral drugs should have the following characteristics: 1) It should cause significant economic loss. Development and use of antiviral drugs could be costly, so savings due to treatment should exceed treatment costs. 2) The disease should not be readily self-limiting. It will not be feasible to treat sub-lethal infections that usually clear up due to normal host immunity. 3) The virus disease should not be fully controllable by vaccines. An antiviral drug may be more suitable than a vaccine that fails to provide complete protection or that has serious side effects. In addition, many livestock producers fail to utilize all available vaccines, thus leading to outbreaks of virus diseases that could have been prevented.

Bovine Viral Diseases

The most appropriate bovine viral diseases for chemotherapy are shown in Table 1. The table also shows the viral agent causing the disease, the type of nucleic acid (deoxyribonucleic acid [DNA] or ribonucleic acid [RNA]) which the virus contains, the family in which the virus is classified, and the status of vaccines for the disease. *Infectious bovine rhinotracheitis* (IBR) affects cattle

around the world. Five forms of disease occur in cattle: respiratory, which occurs particularly in large feedlots; genital, which may lead to infertility in cows; conjunctival, expressed as pink eye, either alone or with the respiratory form; abortion, which can occur any time during development of the fetus; and meningoencephalitis, which usually occurs in young calves. The herpesvirus causing these diseases can become latent and can be reactivated by various stresses. Although relatively effective attenuated vaccines are available for IBR, these vaccines are contraindicated in pregnant animals and latent infections may then occur (Kahrs 1977). Killed vaccines do not give lasting immunity.

Malignant catarrhal fever, also caused by a herpesvirus, is an often-fatal disease characterized by high fever and severe inflammatory and degenerative lesions of the upper respiratory passages, digestive tract, and eyes. It occurs primarily in Africa, but sporadic outbreaks are also reported in North America.

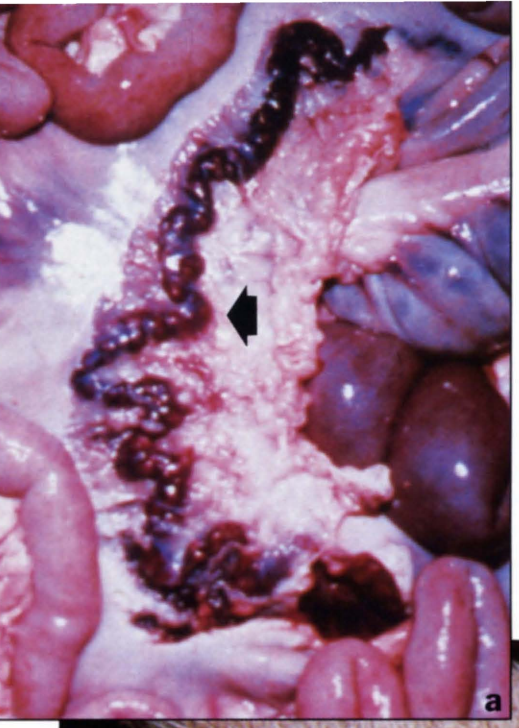
Respiratory distress of newborn calves is caused by several adenoviruses. The type 3 adenovirus is considered to be one of the most important respiratory tract pathogens of cattle, particularly in newborn calves. Other adenoviruses may cause similar respiratory diseases in calves. Weak calf syndrome is also caused by several adenoviruses.

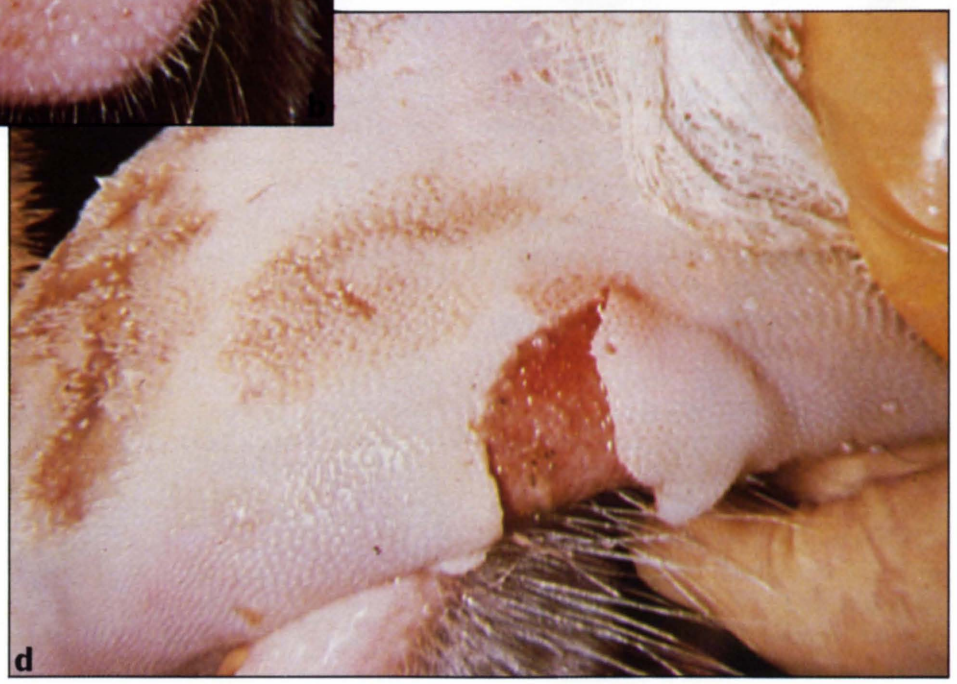
Foot and mouth disease, caused by one of the smallest and, historically earliest recognized viruses, is one of the most feared diseases of animals. It is highly contagious, affects a wide range of animals, and has disastrous effects on livestock production. The estimated cost of controlling a recent outbreak in the United Kingdom was over $600,000,000. Control is difficult because there are many animal hosts, it is very contagious, viral antigenicity varies, and vaccination results in only temporary immunity (Gillespie and Timony 1981). In the

TABLE 1. Target livestock viral diseases for chemotherapy.

Disease	Virus	Nucleic Acid/ Family	Vaccine status
Bovine			
Bovine leukosis	Bovine leukemia virus	RNA/Retroviridae	None
Infectious bovine rhinotracheitis	Bovine herpesviruses 1, 2, and 4	DNA/Herpesviridae	Controversial
Foot and mouth disease	Aphthovirus	RNA/Picornaviridae	Limited usefulness
Malignant catarrhal fever	Bovine herpesviruses	DNA/Herpesviridae	Poor
Vesicular stomatitis	Vesicular stomatitis virus	RNA/Rhaboviridae	Poor
Respiratory distress of newborn calves	Adenoviruses 1-7	DNA/Adenoviridae	Limited usefulness
Scours (calf diarrhea)	Bovine rotavirus	RNA/Reoviridae	Possible vaccine of limited usefulness
Porcine			
Parvovirus infection	Porcine parvovirus	DNA/Parvoviridae	None
Pseudorabies	Porcine herpesvirus	DNA/Herpesviridae	Poor
African swine fever	African swine fever virus	DNA/Iridoviridae	Poor
Swine vesicular disease	Porcine entervirus 9	RNA/Picornaviridae	None
Vesicular exanthema	Vesicular exanthema virus	RNA/Caliciviridae	None
Transmissible gastroenteritis	Transmissible gastroenteritis virus	RNA/Coronaviridae	None
Swine influenza	Swine influenza virus	RNA/ Orthomyxoviridae	None
Ovine			
Bluetongue	Bluetongue virus	RNA/Reoviridae	Controversial
Scrapie	Scrapie virus	?/unclassified	None
Maedi/Visna	Maedi/Visna virus	RNA/Retroviridae	None
Equine			
Foal respiratory disease	Equine adenovirus	DNA/Adenoviridae	None
Equine rhino-pneumonitis, abortion	Equine herpesvirus 1	DNA/Herpesviridae	Difficult to use
Equine arteritis	Equine arteritis virus	RNA/Togaviridae	None
Influenza	Equine influenza virus	RNA/ Orthomyxoviridae	Possibly outdated
Equine infectious anemia	Equine infectious anemia virus	RNA/Retroviridae	None
Avian			
Infectious laryngotracheitis	Fowl herpesvirus 1	DNA/Herpesviridae	Controversial
Transmissible turkey enteritis (bluecomb)	Transmissible turkey virus	RNA/Coronaviridae	None
Influenza (fowl plague)	Avian influenza or fowl plague virus	RNA/ Orthomyxoviridae	None
Avian leukosis/sarcoma	Avian leukosis or sarcoma virus	RNA/Retroviridae	None

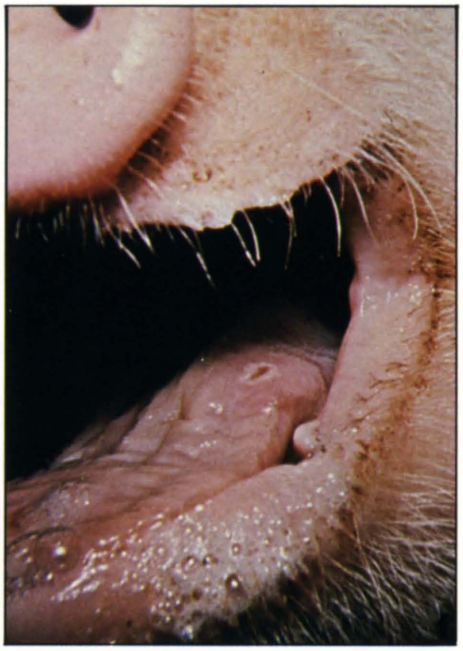
Livestock Viral Diseases: Ailments in Search of Cures





(a) Enlarged mesenteric lymph nodes associated with African swine fever.

Lesions associated with vesicular stomatitis virus on the snout (b), hoof (c), and tongue (d) of swine. The painful tongue lesions inhibit eating, thus leading to significant weight losses.



Lesions associated with vesicular exanthema virus on the snout and tongue of a pig (e). The disease is also associated with semi-discrete tongue lesions and profuse salivation (f), and severe footpad lesions (g).

United States, herd eradication and stringent quarantine procedures are used to control the disease.

Vesicular stomatitis, sometimes called sore mouth of cattle, occurs sporadically in cattle, horses, and swine. It is not usually fatal, but causes ulcers or vesicles on the tongue, in the mouth, and in the nose, resulting in loss of appetite of the animal and associated weight loss. A recent outbreak in Idaho resulted in a lengthy and costly quarantine.

Scours or *calf diarrhea*, a widespread, often fatal disease of calves and other animals, is usually caused by a rotavirus. Vaccines developed for this disease are administered to pregnant cows to protect the newborn calves, but their efficacy may vary within viral serotypes (Mohanty and Dutta 1981).

Porcine Viral Diseases

Table 1 shows potential porcine viral disease targets. *Parvovirus* infections are widespread throughout the world. They primarily cause embryonic and fetal death, abortion, and stillbirths. *Pseudorabies*, caused by another herpesvirus, is particularly serious in swine but also occurs in cattle, sheep, dogs, cats, mink, and other animals. Vaccines exist, but control of pseudorabies, particularly in swine, is difficult and unreliable (Mohanty and Dutta 1981). *African swine fever* is an acute, highly contagious disease confined primarily to Africa, but has begun to occur in the Western Hemisphere beginning in Cuba in 1971. It is now also found in Brazil, the Dominican Republic, and Haiti. *Swine vesicular disease* is very similar to foot and mouth disease. This relatively new disease was first seen in Italy in 1966 and is now spreading rapidly in Europe, the British Isles, Japan, and Hong Kong. It poses a serious economic threat to the United States.

Vesicular exanthema is clinically indistinguishable from foot and mouth

disease. It has not been reported in the United States since 1959, and is now controlled by stringent quarantine and herd slaughter policies.

Transmissible gastroenteritis occurs in swine of all ages, but is particularly fatal to pigs under 5 weeks of age. Vaccines to date have yielded disappointing results. Swine influenza afflicts up to 25 percent of all the pigs in the United States and can also be readily transmitted to man. Secondary infections often cause death.

Ovine Viral Diseases

There are surprisingly few virus diseases of sheep that could be considered as targets for chemotherapy procedures (Table 1). *Bluetongue*, also referred to as *ovine catarrhal fever* or *sore mouth*, is an acute, insect-borne disease characterized by fever, emaciation, oral lesions, and substantial death rate, particularly in lambs. The disease also occurs in cattle.

Scrapie is a slow, progressive disease of the central nervous system which is nearly always fatal. The etiologic agent of scrapie, although thought to be a virus, is not yet classified and is difficult to study. Effective control requires slaughter of all affected animals, and those that have been in contact with infected animals in the previous 3 to 4 years. *Maedi/Visna* are, respectively, respiratory and nervous forms of disease caused by a virus closely related to that which causes acquired immunodeficiency syndrome (AIDS) in humans. Both forms of the ovine disease are fatal.

Equine Viral Diseases

Equine viral diseases which are possible chemotherapy targets are shown in Table 1. *Foal respiratory disease* is a relatively recently discovered disease which is often fatal for young foals. *Equine rhinopneumonitis*, also known as *equine abortion*, is a respiratory disease that occurs most frequently in animals less than 2 years of age. It is not often fatal unless complicated by secondary infections. Effective treatment requires frequent vaccinations.

Equine arteritis is characterized by fever, respiratory distress, excessive nasal discharge and lacrimation. Edematous swelling of the legs, trunk, mammary gland and scrotum are also common, and pregnant mares often abort. The disease occurs principally in the United States. *Equine influenza* occurs throughout the world. Mortality is low in uncomplicated cases but fatalities increase with secondary infections. The infection is very easily spread. Inactivated vaccines are available, but must be properly identified to make sure the vaccine will be effective (Mohanty and Dutta 1981). *Equine infectious anemia* is a progressive, often fatal disease characterized by anemia, progressive weakness, loss of weight and edema. The infection is usually transmitted through insect vectors such as horse flies and deer flies or from the mare directly to the fetus. Antigens of the causative virus vary, so vaccines have not been effective.

Avian Viral Diseases

The avian viral disease targets are shown in Table 1. *Infectious laryngotracheitis* affects the respiratory tract; it lowers egg production and is often fatal. Vaccination can result in a virus carrier state, so vaccination is recommended only in areas where outbreaks have occurred. Eradication of the disease requires complete depopulation and disinfection of the premises. *Transmissible turkey enteritis (bluecomb)* primarily attacks young poults, resulting in dehydration, loss of weight and nearly 100 percent mortality. Egg production drops rapidly. *Influenza* is a common respiratory disease of poultry. In the past, severe epidemics were known as *fowl plague*. A major outbreak recently occurred in the Eastern United States. *Avian leukosis/sarcoma* is a transmissible, virus-induced neoplasm that may have several forms, including lymphoid leukosis, erythroblastosis, myeloblastosis, myelocytosis, and osteopetrosis.

Potential Antiviral Drugs

The drugs effective against certain human virus diseases that have been approved for use in the United States are listed in Table 2. These drugs have potential for use against virus infections of domestic animals. Four of these drugs (idoxuridine, vidarabine, trifluridine, and acyclovir) that have been approved for use against human herpesvirus infections should be considered for treatment of the many herpesvirus-induced infections in veterinary animals. Ribavirin has also exhibited considerable efficacy against certain herpesvirus infections in humans, but is more often used to treat RNA virus infections such as respiratory syncytial disease, influenza and type A hepatitis. Amantadine has been limited to treatment of influenza A infections.

Experimental Studies

Our experiments involve vidarabine and ribavirin. We were the first to discover antiviral properties of these drugs (Sidwell et al. 1969, Sidwell et al. 1972). A typical experiment shown in Figure 1 involves the use of vidarabine against pseudorabies virus in a cell culture system. Cells susceptible to pseudorabies virus were exposed to enough virus to destroy cells or alter cell shape (cytopathogenic effect, CPE) within a 72-hour incubation period. A short time after exposure to the virus, the cells were then treated with various concentrations of vidarabine. After incubation, the cells were examined to assess the degree of CPE. The vidarabine treat-

TABLE 2. Antiviral drugs approved for human use.

Drug name	Generic name	Chemical name	Approved viral disease target
Herplex	Idoxuridine	5-iodo-2′-deoxyurine	Herpes eye infections
Symmetrel	Amantadine	1-adamantanamine hydrochloride	Influenza A
Vira-A	Vidarabine	9-β-D-arabinofuranosyladenine	Herpes eye and brain infections
Viroptic	Trifluridine	2-deoxy-5-(trifluoromethyl) uridine	Herpes eye infections
Zovirax	Acyclovir	9-[(2-hydroxethyloxy)methyl] guanine sodium	Herpes eye, skin, genital and brain infections
Virazole	Ribavirin	1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide	Respiratory syncytial virus infections of infants

ment markedly inhibited the usual viral-induced CPE and reduced virus production.

Similar cell culture experiments involving vidarabine and ribavirin concern other viruses of veterinary importance. The results are summarized in Table 3. Ribavirin, which is unique because of its inhibitory effect on a broad-spectrum of DNA- and RNA-containing viruses, may have the greatest potential in veterinary applications.

The drug is presently approved in the United States for use only as an aerosol to treat respiratory syncytial virus in infants. Our initial studies showed that the drug was moderately effective against respiratory virus infections in laboratory animals when administered orally or by injection, but was much more effective when animals were treated by aerosol (Figure 2). One experiment involved treatment with a micronized powder of the drug that was blown into the nostrils of the animal using compressed freon gas. These and similar experiments led to the development of a compact aerosol generator by researchers with the Baylor University College of Medicine, a device successfully used in ribavirin treatment of patients infected with viral respiratory infections (Knight et al. 1981). We are now studying the use of aerosolized ribavirin to simultaneously treat an entire flock of chickens. Such a form of aerosol treatment would be relatively inexpensive and easy to administer.

Ribavirin has shown some potential in the treatment of retrovirus infections such as bovine leukemia and avian leukemia sarcoma. In cell culture, the compound inhibited syncytium (giant cell) formation induced by bovine leukemia virus and also reduced the development of bovine leukemia virus antigen (Figure 3). Certain retroviruses may produce a variety of malignancies, such as tumors, leukemia, polycythemia, and enlargement of certain organs, in laboratory animals. In one experiment, ribavirin was injected 15

TABLE 3. Viruses of veterinary importance inhibited by vidarabine and ribavirin in cell culture.

Vidarabine	Ribavirin
Turkey herpesvirus	Adenoviruses 3, 19
Mareks disease virus	Turkey herpesvirus
Pseudorabies	Mareks disease virus
Infectious bovine rhinotracheitis	Feline rhinotracheitis
Bovine herpesvirus	Infectious bovine rhinotracheitis
Myxoma	Myxoma
	Influenza A and B
	Parainfluenza, 1, 2, 3
	Newcastle disease
	Vesicular stomatitis
	Rift Valley fever
	Feline calici
	Bovine, porcine rotavirus
	Bluetongue
	Bovine leukemia

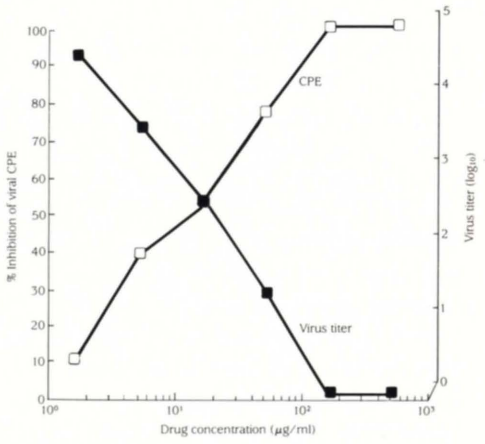


FIGURE 1. Effect of vidarabine on pseudorabies virus in continuous-passaged rabbit kidney cells.

(Adapted from Sidwell et al. 1970.)

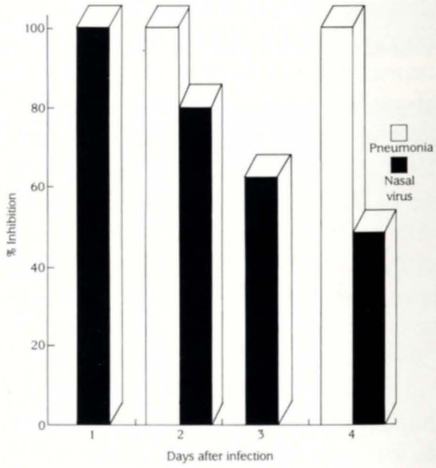


FIGURE 2. Aerosolized ribavirin effect on respiratory virus infections in hamsters.

(Adapted from Sidwell et al. 1975.)

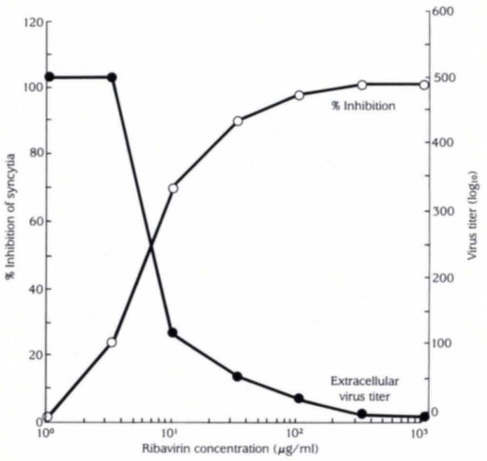


FIGURE 3. Effect of ribavirin on bovine leukemia virus-induced syncytia formation and on viral antigen production in cell culture.

(Adapted from Sidwell and Smee 1971.)

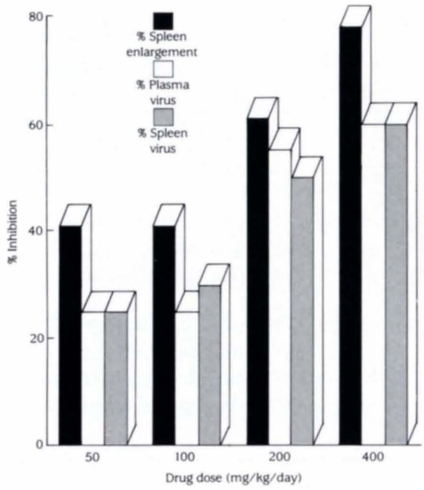


FIGURE 4. Effect of ribavirin treatment on murine leukemia virus infections in mice.

(Adapted from Sidwell et al. 1975.)

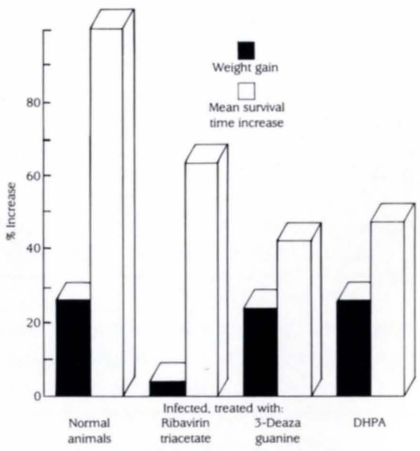


FIGURE 5. Comparison of the effect of treatment with three antiviral drugs on rotaviral disease in infected mice.

(Adapted from Sidwell et al. 1982.)

minutes before the virus was introduced into the animal; the ribavirin injections were repeated 3, 6, and 9 days later. The treatment significantly inhibited splenomegaly and reduced the amount of recoverable virus from the animal (Figure 4), results which suggest that ribavirin may be effective against bovine leukemia and avian leukosis.

Our antiviral chemotherapy studies have also involved treatment of rotavirus-induced diarrhea, or scours, with ribavirin, 3-deazaguanine (an anticancer drug which also exhibits antiviral effects), and 9-(S)-(2,3-dihydroxypropyl) adenine (DHPA), an antiviral compound. The study compared the sensitivity of bovine, porcine, and simian strains of rotavirus to the drugs. Table 4 shows only the relative inhibitory effects of the maximum tolerated dose of each drug. All the viruses were significantly inhibited by each drug; 3-deazaguanine was the most effective. The efficacy of 3-deazaguanine, DHPA, and a triacetate derivative of ribavirin, which is better able to penetrate intestinal cells, against rotavirus-induced diarrhea in mice was also studied. This diarrhea leads to weight loss or failure to gain weight, and is often fatal to infant animals. Oral treatment, particularly with 3-deazaguanine and DHPA, twice daily for 7 days beginning 2 hours before infection had a moderate depressing effect on the disease (Figure 5), as was indicated by increases in weight gain to essentially normal levels and increases in mean survival time of the infected animals. Results indicated that antiviral drugs may effectively treat young animals seriously infected with scours.

Steps to Governmental Approval

Government approval of test compounds involves a series of time-consuming and expensive steps. The procedure to prove that the drug is safe and effective is the same even if the drug has already been approved for human use. Step 1: Numerous experiments are required to show the maximum tolerated dose of the drug and that the drug lacks certain toxic effects such as mutagenicity, teratogenicity, and carcinogenicity. Step 2: It must be proved that acceptable doses of the drug significantly inhibit the manifestations of the disease in the veterinary animal. Step 3: If treated animals are a source of food, it must be proved that the drug does not persist in the tissues or milk. A veterinary investigative new drug (VIND) permit is required before these tests can begin. Our studies have been concerned with this preliminary requirement. Pharmaceutical companies must then apply for the VIND permit to complete the testing procedure.

TABLE 4. Inhibition of rotavirus infection caused by antiviral drugs (cell studies).

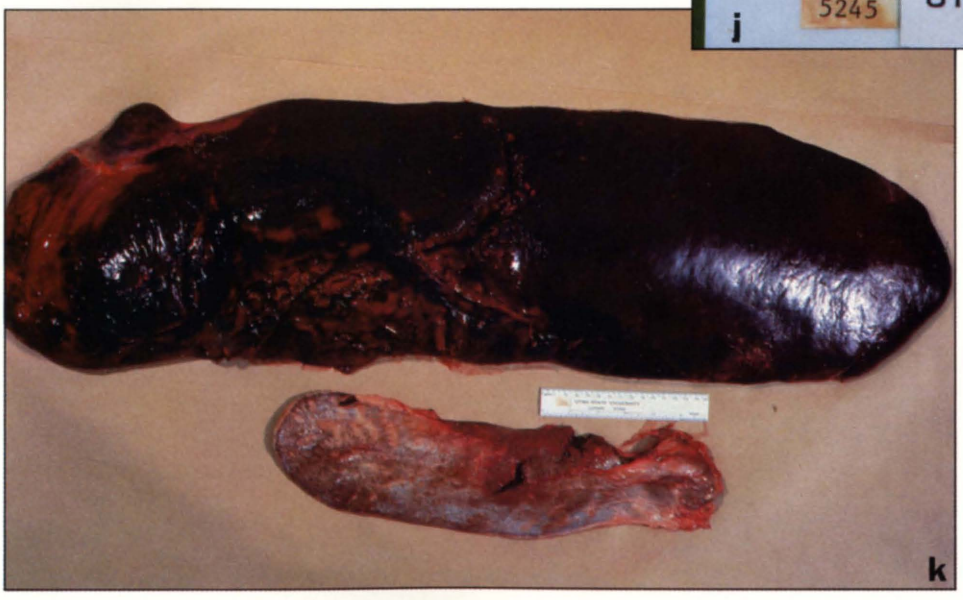
	Ribavirin	3-Deaza-guanine	S-DHPA
	% inhibition		
Bovine rota	80	100	60
Porcine rota	20	70	50
Simian rota	70	100	50

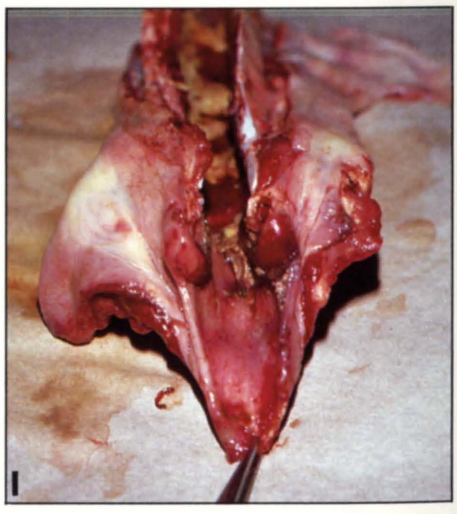
Hepatomegaly (enlarged liver) induced by bovine leukemia virus (h). Left: Infected liver. Right: Normal liver.

Severe lung consolidation (i) in cows infected with bovine rhinotracheitis virus.

Splenomegaly (enlarged spleen) induced by bovine leukemia virus (k). Top: Infected spleen. Bottom: Spleen from an uninfected animal.

Severe congestion in the trachea of a cow infected with bovine rhinotracheitis virus (l).





CHEMOTHERAPY OF VETERINARY VIRAL DISEASES

A special National Academy of Science-appointed committee, formed at the request of the President's Science Advisor, recently released its recommendations concerning the prevention and treatment of viral diseases (Joklik et al. 1986). The report recommended that viral diseases of livestock and poultry be included as potential targets in a national effort to develop vaccines and new antiviral drugs. These recommendations further strengthen our premise that such drugs have great potential for the treatment of viral diseases of animals.

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